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Analgesic action of gabapentin on chronic pain in the masticatory muscles: a randomized controlled trial.

by

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At the beginning of my graduate program someone left this thought stuck on my computer monitor. For some reason I never removed it in the last 2 years and I never asked who left it:

"The guy who takes a chance, who walks the line between the known and the unknown, who is unafraid of failure, will succeed."

– Gordon Parks

I would like to dedicate this work to my grandmother Adel Kimos for setting a firm example of strength, personal integrity, hard work, and above all, excellent sense of humour. I love you.

ABSTRACT

The objective of this study was to evaluate the analgesic action of gabapentin on chronic masticatory myalgia (CMM). This was a 12-week randomized controlled clinical trial, in which fifty subjects were recruited. The outcome measures utilized were pain reported on a VAS, a modified Fricton's Craniomandibular Palpation Index and impact of CMM on daily functioning reported on a VAS. Gabapentin was shown to be superior to placebo in reducing pain reported by subjects and hyperalgesia secondary to palpation in the masticatory muscles. The impact of CMM on daily functioning also appears to be reduced with gabapentin therapy. It can be concluded from this study that gabapentin is effective for the management of CMM.

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LIST OF ABBREVIATIONS

EBM = Evidence based medicine

FDA = Food and Drug Administration

GABA: Gamma-Aminobutropic Acid

GAD = Glutamic acid decarboxilase

CMM = Chronic Masticatory Myalgia

CNS = Central Nervous System

COX1 = Cyclo-oxygenase 1

COX2 = Cyclo-oxigenase 2

MAOI = Monoamine oxidase inhibitors

NPY = Neuropeptide Y

NSAID = Non-steroideal anti-inflammatory drug (s)

PHN = Post-herpetic Neuralgia

PKA = Protein Kinase A

PKC = Protein Kinase C

PLMS = Periodic limb movements during sleep

RCT = Randomized Controlled Trial(s)

RLS = Restless legs syndrome

SSRI = Specific serotonin re-uptake inhibitors

TCA = Tricyclic Antidepressant(s)

TENS = Transcutaneal Electrical Nerve Stimulation

TMD = Temporomandibular Disorder(s)

TMJ = Temporomandibular Joint

chapter 1: INTRODUCTION AND LITERATURE REVIEW

1.1- INTRODUCTION

Orofacial pain affects millions of people every year. The study and diagnosis of orofacial pain encompasses a variety of different conditions, including musculoskeletal problems or temporomandibular disorders (TMD), neuropathic pain conditions and headaches. Chronic masticatory muscle pain is included in the diagnostic classification of temporomandibular disorders (TMD) [1 2]. When masticatory muscle pain becomes chronic, a person's lifestyle and normal activities become affected. Chronic masticatory muscle pain interferes highly with daily activities such as: mastication, laughing, or talking [3]. Chronic muscle pain may also indirectly affect quality of life. Patients suffering chronic pain frequently report symptoms of depression; poor sleep quality and low energy. Ability to maintain employment, normal social activity and interpersonal relationships may also be affected [4].

Chronic masticatory myalgia (CMM), a TMD problem of myogenous origin, is a multifactorial problem that it is thought to be highly influenced by central nervous system (CNS) effects [5 3 6-8], but also by peripheral factors [9-13] and psychological implications [5 14-19]. For this reason the treatment of CMM, as in other chronic pain conditions, is not easy and is often multidisciplinary. Pharmacological approaches are often used to control the pain and provide patients with better daily functioning.

Gabapentin is a new-generation antiepileptic agent that has been widely used in clinical practice and research for different types of chronic pain conditions. This medication is thought to act centrally and it was originally developed to imitate gamma-aminobutropic acid (GABA) but it has been proven not to act on GABA receptors [20]. The use of gabapentin in orofacial pain has been mainly related to treating problems of neuropathic origin and also for migraine prophylaxis [21-23]. It has not been tested to treat chronic musculoskeletal pain in the orofacial pain region or other parts of the body. What is known of its central mechanism of action is suggestive of having a potential role in treating chronic pain of musculoskeletal origin, such as CMM.

This chapter presents the goals of this study and a comprehensive literature review. The literature review in this thesis is divided in two main parts. The first part involves the prevalence, pathophysiology, clinical implications and management options of CMM. The second part addresses what it has been demonstrated and proposed about gabapentin for its use in chronic orofacial pain, including its mechanism of action and implications in clinical management.

1.2- PROBLEM STATEMENT

Chronic pain represents an important problem in the community, affecting general health, psychological health and social and economic well being [4]. Chronic pain in general is self-reported by 50.4% of the general population [24] and is estimated to represent the third largest health problem in the world [4]. In addition, chronic pain patients use health care services up to five times more frequently than the rest of the population [25 26], representing millions of dollars of additional cost to the health care system every year [4].

Chronic pain can be of different types such as neuropathic, visceral, vascular, neurovascular and musculoskeletal. It is reported that about 16% of the adult population are affected by severe musculoskeletal pain [27]. Musculoskeletal chronic pain can be generalised, meaning that it is found all over the body (e.g. fibromyalgia) or regional, only affecting one area (e.g. facial pain). It has been reported that 40% of all chronic pain cases seen in pain clinics are located in the craniofacial and cervical regions [28], constituting orofacial pain conditions.

An important part of orofacial pain problems is represented by temporomandibular disorders (TMD). TMD is a musculoskeletal condition that is present in approximately 40 to 60% of the general population and includes articular and/or muscular problems of the masticatory system [2 3]. Pain in the masticatory muscles can become chronic, representing a regional problem that shares many features with other chronic pain conditions [16]. Like many other chronic pain problems, chronic masticatory myalgia (CMM) has been considered to be a multifactorial problem, with great part of influences derived from central nervous system (CNS) effects on the peripheral pain perception in the masticatory muscles [5 29 30 3]

The treatment of CMM is not easy. This condition has a multifactorial origin; therefore the management strategies are often multidisciplinary. Pharmacological therapy is one of the most commonly used strategies to manage and minimise the chronic pain as much as possible and maximise the patient's function and quality of life. Despite the large body of literature, few studies have evaluated pharmacological treatments for TMD in a well-controlled fashion. The population with TMD is heterogeneous and past studies often do not distinguish musculoskeletal from

articular pain. A need exists for well-controlled studies of drugs used for chronic orofacial pain of musculoskeletal origin in the relevant patient population. These trials should account for periods of administration that approximate their use in the clinical practice, adequate indexes of side effects and a comparison with a group treated with placebo in order to control for cyclic fluctuations of symptomatology.

Unfortunately, the pharmacological options to treat CMM are limited. In clinical practice, drugs like acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) do not achieve significant pain reduction levels when treating CMM. Opiates help to reduce pain but are not often well tolerated by many patients due to their side effect profile [31]. Tricyclic antidepressants (TCA) have been widely used with more successful results to manage chronic musculoskeletal chronic pain in general and in the orofacial region [32-36].

Antiepileptic agents have also represented a pharmacological option to treat orofacial pain problems, mainly of neuropathic origin. In comparison to other drugs such as opiates and TCAs, new generation antiepileptic agents appear to have a more favourable profile of side effects and also to be beneficial for orofacial pain [37].

Gabapentin is a new generation antiepileptic agent that was initially developed as a gamma-aminobutropic acid (GABA) analogue, but does not directly act on GABA receptors [20]. Although the analgesic mechanism of action of this drug on the CNS is not yet known, gabapentin is used for different types of central chronic pain conditions, such as post-herpetic neuralgia (PHN) [38]. It has been also reported that gabapentin can produce pain reduction in patients experiencing chronic

musculoskeletal pain [39]. This medication has been used for CMM and widespread chronic musculoskeletal pain in the clinical practice, obtaining good clinical outcomes. However, these are empirical trials since there is no research evidence in the literature assessing gabapentin's action on CMM.

To date there are no randomised-controlled trials (RCT) evaluating the analgesic effect of gabapentin specifically on CMM. We aimed to evaluate a possible role of a central acting drug like gabapentin as a potential analgesic on these patients. This could constitute a new beneficial tool for the treatment and management of CMM, improving the patients' symptoms with a milder profile of adverse reactions. The appropriate treatment of chronic pain patients would eventually lead to better quality of life, a more positive contribution to society, and less of a long-term drain on the health care system resources [4].

1.3- RESEARCH QUESTIONS

1) Is gabapentin more effective than placebo at reducing CMM pain intensity reported by subjects?
2) Is gabapentin more effective than placebo at reducing hyperalgesia on extraoral palpation of the masticatory muscles in subjects experiencing CMM?
3) Is gabapentin more effective than placebo for reducing the impact of CMM on the patient's quality of life and daily functioning?

Additional question: (If there is pain reduction after the treatment)

Is CMM pain reduction reported by subjects associated with decreased hyperalgesia on extraoral palpation of such muscles?

1.4- HYPOTHESES

1.4.1- Null Hypotheses

1) Gabapentin is equally or less effective than placebo for reducing chronic masticatory muscle pain intensity reported by subjects.
2) Gabapentin is equally or less effective than placebo for reducing pain on extraoral palpation of the masticatory muscles in those subjects experiencing chronic masticatory myalgia.
3) Gabapentin is equally or less effective than placebo for reducing the impact of chronic masticatory myalgia in the patient's quality of life and daily functioning.

1.4.2- Alternate Hypotheses

1) Gabapentin is more effective than placebo for reducing chronic masticatory muscle pain intensity reported by subjects.
2) Gabapentin is more effective than placebo for reducing pain on extraoral palpation of the masticatory muscles in those subjects experiencing chronic masticatory myalgia.
3) Gabapentin is more effective than placebo for reducing the impact of chronic masticatory myalgia in the patient's quality of life and daily functioning.

1.5- LITERATURE REVIEW

1.5.1- CHRONIC MASTICATORY MYALGIA (CMM)

CMM is a continuous muscle pain condition that is a sub-classification of the masticatory muscles disorders within the TMD family [3]. TMD is a general term that includes a variety of clinical problems of the masticatory muscles and the temporomandibular joint (TMJ) and are considered a major cause of non-dental pain in the orofacial pain region, and also a subgroup of musculoskeletal disorders [1]. Masticatory muscle disorders involve diagnostic subgroups that have been classified as acute myalgic disorders and chronic myalgic disorders [3]. Chronic myalgic disorders include myofascial pain, chronic masticatory myalgia, and chronic systemic myalgic disorders.

The International Association for the Study of Pain (IASP) [40] defined chronic pain as that pain which persists past the normal time of healing, which is considered to be anytime from one to six months. CMM can be defined as constant pain in the masticatory muscles for at least six months. Like other chronic pain conditions, CMM may present Axis II factors representing psychosocial consequences [2 41].

1.5.1.1- PREVELANCE OF CMM

To date, there are no epidemiological studies specifically evaluating the prevalence of CMM in the general population. However, CMM is a temporomandibular disorder and there are many studies

reporting the prevalence of TMD in general [42 43 44-58] without specifying the percentage of patients specifically presenting CMM. These studies report an average of 40 to 60% of the population as presenting at least one sign of TMD. It is reported by one study [59] that 33% of patients with TMD present a combination of myalgic and articular disorders, and another 33% purely masticatory muscle pain, but unfortunately it is not differentiated whether the muscle pain was truly a chronic condition or an episodic problem.

The incidence of TMD is reported to be especially pronounced in patients between 20 and 40 years of age [53 60 61]. TMD signs and symptoms tend to be fewer in children than in adults, since they tend to increase in frequency and severity in the second and third decade of life [48 52 62]. It is also reported that TMD is significantly more predominant in females than in males [42 51-54 62-65] with a 3:1 ratio [2].

It is also important not to forget that those patients experiencing fibromyalgia may present CMM as part of their overall symptoms. The incidence of fibromyalgia in the general population has been reported to be 2%, starting at any age and being seven times more common in women than in men [66].

1.5.1.2- ETIOLOGY OF CMM AND GENERAL OVERVIEW OF THE PATHOPHYSIOLOGY OF CHRONIC PAIN

In chronic pain, more than one mechanism is usually involved, which may vary from patient to patient and may change with time. Normal sensory function is the result of the equilibrium

maintained by the activity between neurones and their environment. Any disruption of this equilibrium derived from changes in sensitivity, excitability, information transmission, growth status, and survival can lead to serious changes in sensory function.

The most common initial event leading to CMM is prolonged muscle soreness and/ or regional myofascial pain in the masticatory muscles [3]. This can be a consequence of trauma to the masticatory system, which can be micro or macrotrauma that would eventually lead to local tissue damage. It is expected that tissue damage produces pain inputs to the brain, but once healing takes place, pain signals should stop, making pain symptoms subside [1 67]. However, in some occasions the pain continues regardless the healing of the tissue in the masticatory muscles. The longer the time of constant masticatory muscle pain, the greater the risk of developing CMM. More than the duration of the pain complaint is the continuity of such pain what would ultimately determine the onset of CMM. Episodic pain events occurring for prolonged periods do not tend to lead to CMM as much as constant pain with no intermission periods in between [3].

The pathophysiology of CMM and other chronic musculoskeletal conditions is not completely understood and remains controversial. It is though to be a problem with a multifactorial origin and pathophysiology. There is no consensus in the literature regarding the pathophysiologic pathways mediating this condition [68 69]. There is a lack of studies assessing the specific pathophysiology of CMM. An important part of the literature proposes that this condition is mediated by central sensitization effects that lead to a peripheral perception problem in the masticatory muscles [3 5 6 8 29 30 70-74].

On the other hand, there are other studies and literature reports, which propose that chronic orofacial pain of muscle origin may also be originated by other causes. Psychological factors have been implicated with the inset of chronic orofacial muscle pain and other chronic musculoskeletal problems like fibromyalgia. Stress somatization has been implicated in the onset and mediation of chronic muscle disorders [70 5 14-18 18 19 75-80]. Patients with a history of sexual abuse and post-traumatic stress disorders have been related to chronic TMD pain [81 3 82].

Besides psychological factors and central factors, chronic masticatory muscle pain has been also associated to peripheral problems such systemic and chronic local infectious conditions in the masticatory muscles [83-86]. Other local substances such as nerve growth factor (NGF) [12 87], inflammatory substances [9 88] and peripheral release of serotonin [10] have been histologically detected in master muscles of patients with chronic masticatory muscle pain, and therefore associated with the maintenance of such pain.

Chronic muscle pain disorders may have central and peripheral pain mediatory components that occur simultaneously [89]. It is reported in the literature that patients with chronic muscle pain may also present local myofascial trigger points [70] that have been associated with local hypoxic changes [90-92] and ischemia [70] in the muscle tissue. In addition, it has been reported the presence of inflammatory mediators in the masseter of patients with chronic pain and fibromyalgia [11], suggesting that inflammation may be a local pain component that coexist with central pain mediation in these patients. However, other studies contradict these results demonstrating no histological presence of inflammation in samples of muscles with chronic pain [93 94].

In summary, it can be appreciated how there is no definitive consensus in the literature regarding the aetiology and pathophysiology of chronic muscle pain. Although this type of pain appears to have a strong influence from CNS effects, other psychological peripheral conditions have also been implicated.

1.5.1.2.1 **Neuroanatomy of CMM**

In most of the human body, pain transmission from the periphery to the brain cortex is addressed through the integration at three levels within the CNS: the spinal cord, brainstem and forebrain [95]. In the orofacial region there is a different anatomic arrangement, since those afferent impulses carried by the trigeminal nerve enter directly into the brainstem to synapse in the trigeminal spinal nucleus. This area presents a very similar structure of the dorsal horn of the spinal cord and is considered an extension of it [1 2 6 7 96 8].

Two main areas compose the brainstem trigeminal nucleus complex: the main sensory trigeminal nucleus, which receives pulpal and periodontal afferent fibres, and the spinal tract, which is subdivided in three nuclei: the subnucleus oralis, subnucleus interpolaris and subnucleus caudalis. These three subnuclei receive pulp afferents, but the subnucleus caudalis is the area that has been especially implicated with receiving afferents from the craniofacial muscles and face skin [6 97 7]. In fact, it is reported in the literature that the subnucleus caudalis is an equivalent area to the substantia gelatinosa of the spinal dorsal horn [2 7], which is a highly important area of pain transmission and central sensitisation mechanisms.

In the subnucleus caudalis, second order neurons behave similarly to those in the spinal dorsal horn. In this area, only a few neurons receive specific nociceptive input from deep tissues, and many nociceptive neurons have convergent input from several areas, including the TMJ, masticatory muscles, facial skin, oral mucosa and cervical viscera (i.e. larynx) [7 71]. These cells are located in the superficial layers (laminae I and II) and deep layers (laminae IV and V) of the subnucleus caudalis, which are equivalent to the superficial layers of the dorsal horn in the spinal cord [7].

On the other hand, descending analgesic systems are believed to originate from cortical neurons and neurons of the amygdala, which carry survival-relevant information in order to modulate pain. This descending analgesic system is mediated in part by the periaqueductal gray area, where the cortical neuron synapses with a second neuron. This second neuron projects to the rostroventral medulla, where makes synapses with a third neuron that descends to the dorsal horn of the subnucleus caudalis. This pathway, including the periaqueductal gray, rostroventral medulla to spinal cord mediates opiate –dependent descending analgesia [98].

1.5.1.2.2 **Ascending mechanisms of pain transmission in CMM**

Peripheral Sensitization

The features of damaging stimuli are encoded by receptors located in peripheral tissues of the masticatory muscles called *nociceptors*. All nociceptive fibres conduct impulses along finely

myelinated on unmyelinated neuron fibres from the periphery to the subnucleus caudalis. There are two types of nociceptors: Aδ fibres and C fibres.

A - receptors are small myelinated fibers subdivided in three families: Aα , Aβ and Aδ fibres. Aα axons are associated with sensory proprioception of muscles and joints, and Aβ fibres are cutaneous mechanoreceptors [98]. Aδ fibres are in charge of pain information transmission. Since they are myelinated, Aδ nociceptors are fast conduction fibres and usually transmit the "first pain".

C fibers are small, non myelinated and slow conduction nociceptors. They have higher impulse threshold than Aδ fibers [98] and account for most of the nociceptive afferents [99 100]. C fibers are called polymodal nociceptors because they are also associated to mechanical, thermal and chemical stimuli responses [98 101].

Once tissue damage occurs and nociceptors are activated by noxious stimuli, a local inflammatory process begins in the affected site [8]. Following cell injury, arachidonic acid is released form phospholipids located in cell membranes. Two enzymes, cycloxigenase and lipoxygenase influence the metabolism of arachidonic acid. Cycloxigenase converts arachidonic acid into prostaglandins, which induces an increase of vascular permeability, activates leukocyte migration to the affected site and sensitizes nociceptors. On the other hand, lipoxygenase induces the formation of leukotrienes, which also increase vascular permeability, and chemotaxis of polimorfonuclear leukocytes. Leukotriene B4 facilitates the release of chemicals from leukocytes which provokes nociceptors sensitization [102].

The enzyme cycloxigenase has two isoforms, cycloxigenase 1 and 2 (COX1 and COX2). COX1 is associated with the regulation of gastric acid and kidney function. COX2 is associated with inflammatory mediators' synthesis such as prostaglandins. Prostaglandins evoke nerve sensitization and nociception in nerve terminals by acting on G protein coupled receptors, known as prostanoid receptors, located in the sensory neurons [103-105]. This leads to an elevation of cyclic adenosine monophosphate and the subsequent activation of protein kinase (PKA), initiating sensory neuron sensitization. This results in membrane excitation and enhancement of calcium channels currents [103].

Bradykinin is also another important inflammatory mediator. When tissue damage occurs, the precursor of this mediator, which circulates in blood, is activated and converted to bradykinin to be released into the affected site. Bradykinin increases vascular permeability, vasodilatation, and leukocyte chemotaxis. This mediator also activates nociceptors and this action is potentiated by prostaglandins already present in the affected tissue [102].

Substance P, an 11-aminoacid peptide, is another important mediator synthesized in cell bodies in the dorsal root ganglion and then transported peripherally to sensory terminals [101]. Substance P is released from the peripheral endings of nociceptors after their activation, promoting plasma extravasation and the release of histamine from mast cells and serotonin from platelets, which contribute in nociceptors sensitization [102 106]. Peripherally, substance P also causes the activation of other inflammatory cells like macrophages, monocytes and lymphocytes [106].

Catecholamines (adrenaline and epinephrine) are also involved in the sensitization of peripheral nociceptors. The activity of polymodal nociceptors is also modulated by catecholamines. In addition, an increased number of alpha-adrenergic receptors in small diameter fibers after nerve injury has been reported [101]. Other factors such as the cytokines (interleukins, interferon, and tumour necrosis factor) are involved in the inflammatory process. These substances are released by phagocytes and leukocytes [106].

In the site of inflammation, a cytokine called interleukin 1-beta and tumour necrosis factor alpha induce Nerve Growth Factor (NGF) production from fibroblasts and keratocytes. NGF activates the release of histamine and serotonin from mast cells and increases the synthesis of substance P. These events participate in the sensitization of nociceptors and hyperalgesia [96].

C-fibres also express vanilloid receptors, which are involved in the nociceptor sensitization. They are activated on repeated noxious stimulation. Vanilloid receptors participate in the sensitization of thermal and inflammatory pain and are non-selective cation channels. Sensitization is mediated through either increases in intracellular calcium levels or activation of intracellular kinases [95]. In addition to these inflammatory processes, it has been demonstrated that the activation of peripheral excitatory amino-acid receptors, such as N-methil D-aspartate (NMDA) receptors in the masseter muscle, plays an important role on firing afferent excitation in masticatory muscle pain [107] [108].

Once all these peripheral mechanisms occur, sensitization of the afferent nerve endings takes place. This condition can progress to an inflammation of the neuron cell itself, called neurogenic inflammation.

Neurogenic Inflammation and Wind-up as the start-point of central sensitization

A prolonged increase in excitability of the nociceptors may occur to the point where they become more responsive to noxious stimulation, and also start responding to stimuli that are normally innocuous. This process of peripheral sensitization would lead to subsequent hyperalgesia and allodynia [8]. Small-diameter primary afferent neurons not only transmit nociceptive messages to central neurons, but also play an important role in inflammatory responses in the periphery through axon-reflexes mechanisms, known as neurogenic inflammation [109]. Noxious heat stimulation of the skin of rat hind paw induces release of substance P and calcitonin-gene-related peptide from small-diameter primary afferent fibers. The release of these neuropeptides in the periphery are associated with edema and thermal injury reaction [110 111]. Inflammation within the neuron or ganglion may also elicit neuron alteration by introducing new chemical messengers that alter the function, chemistry and survival of cells [112]. Neuropeptide Y (NPY), acting on peripheral Y1 receptors of C-fibers, mediates this release of substance P in neurogenic inflammation [113]. However, when pain becomes chronic, neurogenic inflammation may be altered. After large amounts of substance P are continuously released from peripheral neurons, down-regulation of the number of neurokinin receptors and their effectiveness takes place in the periphery. This may induce a reduction of the flare response to peripheral stimulation [109].

Wind-up is another mechanism that induces central sensitization [114]. This process consists of a low-frequency-dependent increase of the action potential discharge produced by C-fibers upon repetitive stimulation, and is often of short duration [114-117]. This process reflects a decrease of GABA in superficial laminae of the dorsal horn [114 117] and activation of second messenger cascades (adenosine, protein kinase C and proteine kinase A) that posphorilate NMDA receptor channels [115]. These events may also be reinforced by the entry of calcium and sodium into the cell [96 118] ,the activation of neurokinin receptors and the generation of peptidergic slow synaptic potentials. This event may result in subsequent C-fiber stimulation, which induces a progressive action potential output from central pain-projecting neurons. [118].

Central Sensitization

Central sensitization is the final sum of many of the hyperexcitability physiological phenomena occurring in the dorsal horn and subnucleus caudalis. It involves a variety of neuroplastic changes of the CNS that would lead to an expansion of mechanoreceptor field [73], resulting in allodynia and hyperalgesia of the masticatory muscles [73 73]. Altered physiology of peripheral nerves, impacts the physiology of the dorsal horn so that pain becomes centralized [114 118]. Central sensitization can be manifested in three different ways: enlargement of the area in the periphery where the stimulus will activate neurons, increased response to supra-threshold input and the initiation of action potential discharge by sub-threshold input [112].

Signals from peripheral nociceptors travel along the smallest nerve fibres and terminate in the dorsal horn of the spinal cord and in the subnucleus caudalis in the head area [6 96]. The terminals of these fibres release a number of chemical mediators associated with pain information.

Ectopic firing of subnucleus caudalis neurons is critical in originating and maintaining central sensitization. This ectopic activity is partially induced when the normal expression of neuropeptides becomes affected. Peripheral tissue injury increases substance P, neuropeptide Y (NPY) and calcitonin gene-related peptide release in the spinal cord [96 116] and subnucleus caudalis [96]. These neurotransmitters act at ionotropic receptors and G-protein coupled receptors, leading to an increased hyperexcitability of the subnucleus caudalis neurons [96]. An inappropriate release of these neurotransmitters from primary afferent neurons contributes to increase of neuronal excitability that takes place along with centralization of pain.

Another factor that highly influences central sensitization in muscle tissues of the craniofacial region is the neuroplasticity and convergence of nociceptive neurons [8 71 72]. These neurons, present in the subnucleus caudalis of the trigeminal brainstem, also receive additional inputs from afferents supplying other tissues such as the skin and dental pulp. Such features are thought to underlie the poor localization, spread and referred pain that is characteristic of chronic TMD problems [71]. These nociceptive inputs appear to be especially accentuated when neuroplastic changes of the peripheral neurons take place in the muscle tissue, including prolonged responsiveness to afferent inputs, increased receptive field size and ectopic firing activity [71].

Several neurotransmitters are involved in the pain information transmission in the dorsal horn. Glutamate is one of the most important excitatory neurotransmitters and has an important role in the spinal mechanisms of pain transmission [8]. Unmyelinated C-fibers release glutamate as their neurotransmitter when activated by noxious stimuli. This neurotransmitter acts post-synaptically in

amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors to cause a rapid depolarization in the neuron membrane and in NMDA receptors [72].

NMDA receptors act as key elements in the process of central sensitization in CMM [8 72 73 119]. They are normally closed at resting membrane potentials because a magnesium ion blocks the channel pore to avoid glutamate binding and further activation. However, prolonged neuronal depolarization induces the opening of this channel by substance P. Substance P has an important role on central sensitization since it acts on neurokinin 1 receptors, extending depolarization, and increasing intracellular calcium concentration [7]. This process activates protein kinase C that acts on the G protein-coupled receptor and phosphorilate the NMDA receptor, removing the magnesium block [7 101]. This event allows the entrance of calcium influx into the neuron, increasing its hyperexcitability [112]. In addition, calcium also enters the postsynaptic neuron via voltage calcium channel [95], inducing second messenger cascades, such as adenosine, protein kinase C and protein kinase A [112]. Together, all these events increase the excitability of the neurones located in the subnucleus caudalis, which become more responsive to all its inputs, leading to central sensitization [106].

In addition, it is reported that NMDA receptor activation and the subsequent calcium influx result in generation of nitric oxide, by the activation of the nitric oxide synthaze enzyme. Nitric oxide is believed to be a retrograde transmitter feeding back from spinal neurons to presynaptic sites to further increase neurotransmitter release [115]. NMDA receptors activation leads to a subsequent cascade of pain transmission events that would complete the central sensitization process.

Repetitive action potentials induce changes in the expression and function of sodium channels in the cell membrane, which causes more membrane depolarization. This would also induce changes

in the expression of calcium channels, which are the key to neurotransmitter release. Ongoing peripheral stimulation may evoke an increased activity of neurotransmitter release by primary afferent fibres, especially if there is also plasticity in calcium channel function[120]. It has been suggested from experimental pain models, that there is a reduction of the expression of functional calcium channels and increased inactivation of the few ones that are actually expressed. Such events contribute significantly to ongoing excitability that takes place in certain chronic pain states [121], such as CMM.

There are different types of calcium channels, including L-, N- and P/Q-types. N- and P-type voltage dependent calcium channels are widely expressed through the brain and spinal cord. The N-type calcium channel appears to be mainly involved in the pre- and postsynaptic information processing and is concentrated in laminae I and II of the dorsal horn. These calcium channels are activated by strong membrane depolarization, permitting calcium influx in response to action potentials. In consequence, secondary neurotransmitter release occurs. For this reason, calcium channels are considered a major link between neuronal excitability and synaptic transmission [121].

In addition to high voltage activated calcium channels, low-voltage-activated calcium channels (T-type channels), exist in both neuronal and non-neuronal cells. These channels are activated at voltages near the resting membrane potential and do not alone support neurotransmission. However, T-type calcium channels are involved in the regulation of cell excitability [121]. It is reported that T-type calcium channels are capable of generating a large postspike of depolarization, which represents a powerful mechanism for triggering ectopic activity [114].

NPY is another neurotransmitter that influences calcium channels activity. NPY acts in Y-1 receptors coupled to L-type calcium channel currents expressed in presynaptic neurons. Selective activation of Y-1 receptors or application of NPY increases high-voltage calcium currents in peripheral neurons [117]. Therefore it has been suggested that Y1 antagonist could be an effective strategy for the treatment of peripheral neurogenic inflammatory diseases [113].

The mechanisms just described are responsible for maintaining continuous stimulation of the ascending pain pathways in chronic pain. However, decreased function of descending pain mechanisms is also involved.

1.5.1.2.3 **Descending Mechanisms of pain modulation in CMM**

The normal physiology of the descending system is to modulate the afferent pain transmission. The descending system is activated by ascending input after tissue injury. This ascending and descending loop is activated upon prolonged stimulation. An increased neurotransmission of excitatory amino acids activating NMDA receptors would lead to an activation of the descending control system [122]

Descending facilitation and inhibition

The central pathway of the descending system is composed by two subsystems: the facilitation and the inhibition system. The descending facilitation system is activated immediately before nociceptive response and is mediated by *on-cells*. The descending inhibition system is associated with inhibition of nociceptive behaviour and is mediated by *off-cells*, which express a pause in their

firing just prior to nociceptive response. Both on-cells and off-cells are considered pain modulator neurons located in the rostroventral medulla. What appears to be important is the balance between synaptic excitation and inhibition under different conditions. It is possible that severe persistent pain is established when the facilitation system activity overrides the inhibition [122].

The participation of descending activity appears to build up gradually after tissue injury. In the first hours of inflammation the afferent input and descending facilitation take action. After few hours, descending inhibition start increasing while descending facilitation decreases [96 122]. These changes are the result of NMDA activation by excitatory neurotransmitters and the plasticity of the neurons in the rostroventral medulla. It has been showed that the number of on-cells increases during inflammation and off-cells start increasing after the inflammatory process [122].

Descending neurotransmitters

The activity of the nociceptive neurons of the trigeminal brainstem can be modulated by the descending influence from other brainstem structures and higher brain centers [8]. The descending system presents different neurotransmitters, which are related with pain inhibition and modulation. They help to modulate and counteract the ascending pain transmission.

GABA is a major inhibitory neurotransmitter in the brain. GABA decreases neural membrane action potential and therefore decreases nerve excitability [37]. This neurotransmitter is present in diverse inhibitory interneurons and projection neurons in the brain. The arrival of depolarizing stimuli, such as an action potential in a presynaptic terminal, activates a process, which results in liberation of

GABA into the synaptic cleft [98]. GABA can be released from neural tissues by either calcium-dependent or calcium-independent mechanisms [20]. GABA receptors are subdivided into GABA-A and GABA-B. GABA-A receptors are a ligand gated chloride channel and mediate the bulk of inhibitory synaptic transmission. GABA-B receptors, a G protein coupled receptor, are localized both presynaptically, where they inhibit neurotransmitter release, and postsynaptycally, where they mediate a slow inhibitory response [98].

Glycine is another important inhibitory neurotransmitter. Glycine is an amino acid that is used for protein synthesis in the body. However, a small fraction of the glycine pool of the body is packed into synaptic vesicles in certain neurons to be released as a neurotransmitter. The arrival of an action potential in the presynaptic terminal of a glycinergic neuron induces glycine release to the presynaptic cleft, where is free to diffuse and bind with its receptors located on postsynaptic face of adjacent cells. Glycine receptors are mainly restricted to the brain and spinal cord and, as with GABA receptors, are ligand-gated chloride channels [95 98].

Serotonin and noradreline are also involved in descending pathways. Neurons that produce and release serotonin are mainly located in the brain stem, and its projections can reach the cortex and limbic structures. Serotonin has an important analgesic action when it binds to 5HT receptors located in the nerve terminals [98]. Noradreline also has an analgesic activity in the descending system and its receptors are the α-2 adrenoreceptors.

Another important group of substances participating in pain inhibition is endogenous opioids. Endogenous opioids are neuropeptides that can range from 2 to 30 amino acids in length. There

are three major families of opioids in the brain: the enkephalins, the dynorphins and the endorphins and they are peptide products of three different genes [102] [123]. The main function of endorphins is to depress activity in the cerebral cortex and the thalamus. They have an amazing similarity to morphine which has been demonstrated by the fact that naxolone (morphine antagonist) decreases analgesia of natural endorphins and morphine. There are also three major types of endogenous opioids receptors: μ (mu), δ (delta) and *k* (kappa). Opiates receptors are located on the nerve terminals of the sensory afferents in the spinal cord and brain [124]. Endogenous opioids have also been shown to be involved in hormonal and psychological functions.

Enkephalins consist of 5 amino acids. There are two different structures for enkephalins, which differ in the terminal amino acid. One has methionine (Met-enkephalin) and the other has leucine (Leu-enkephalin) [125]. Enkephalins released from neurons inhibit the release of substance P by synapsing between the terminal end of one neuron and the receiving surface of another pain transmitting neuron. Leu-enkephalin interacts preferentially with the δ-receptors and Met-enkephalin interacts with both μ-receptors and δ-receptors [124]. The main location of enkephalins is in the globus pallidus, striatum, hypothalamus, midbrain nuclei and dorsal horn of the spinal cord [125]. Enkephalins are rapidly hydrolysed and their half life in plasma is about one minute [124].

Endorphins are larger neuropeptides with 30 or more amino acids. Endorphins can be classified in β-endorphins, δ-endorphins, γ-endorphins, α-endorphins [125]. μ-receptors and δ-receptors are the predominant acting site of β-endorphins [123]. When endorphins bind to these receptor sites, they disrupt pain pathways and less pain is felt as a result. μ-receptors are the target site for opioid

drugs, such as morphine, which mimics the effect of endorphins. β-endorphin is produced by cells of the non-pituitary and periaquate regions of the hypothalamus. Fibers containing β-endorphin project from the hypothalamus thalamus, limbic system mescenecephalon and telencephalon [125].

Dynorphins possess a similar chemical structure to enkephalins, but they are much more potent and mediate more sedative actions at the cortical level. Dynorphins induce their inhibitory effect by binding to *k*-receptors. Dynorphins inhibit the release of substance P after an acute noxious stimulus [126]. There are elevated levels of dynorphins in striatum, hypothalamus, frontal and occipital cortexes and lumbar area of the spinal cord. However, there is lower number of *k*-receptors in the spinal cord, compared with other opioid receptors [123].

It is important to point out that μ-receptors are sub classified in μ1 and μ2. μ1 receptors are responsible for analgesia and μ2 receptors have been implicated in causing respiratory depression and constipation. Morphine binds to μ1 and μ2 receptors, while enkephalin binds preferentially to μ1 and δ-receptors. It is important to develop highly selective opiate drugs that only bind to the μ1 receptor, in order to reduce side effects associated with μ2 receptors.

It has also been reported that endogenous opioids can have peripheral action in the site of tissue injury, which is associated with the immune system. Peripheral tissue injury causes a migration of immune cells containing β-endorphin and met-enkephalin to the inflamed site [127] [128]. The immune cells dynorphin release and its action in inflamed tissues has also been reported [128] [129]. β-endorphin is contained predominantly in the memory-type T cells [127] [129]. The release and action of these peptides in the sensory nerve terminals induces endogenous analgesia. It has also been

suggested that there is a feedback mechanism between central and peripheral endogenous pain control, since an effective central inhibition of pain would reduce the need for opioid-containing immune cells migration to the affected site [127]. In this way, the immune system prevents the excitation of sensory peripheral neurons before nociceptive stimuli can reach more central sites [129] [128]. This shows how the immune system plays an important role in peripheral pain control.

Changes in descending mechanisms and their relationship to central sensitization in CCM

The dynamic changes in descending mechanisms can be followed chronologically after tissue injury and inflammation. In early inflammatory stages there is a predominant role of descending facilitation systems. Days later, there is an increase of descending inhibition and decrease of descending facilitation in order to counteract continuous noxious input [122]. The time-dependent functional changes in descending inhibition are, in part, mediated by increased excitatory amino-acid release [130].

Descending modulation and descending plasticity are normal functions of the brain and are considered to be protective mechanisms. However, injury to neural tissue can upset the balance between descending facilitation and inhibition [122], leading to pathological consequences [7]. The protective increased descending facilitation mechanism that is normally triggered after tissue injury can become a source of persistent pain [122]. Therefore, the maintenance of hyperalgesia in persistent pain is dependent on such facilitation system instead of inhibition mechanisms. The imbalance between these modulatory pathways is considered to be one of the mechanisms underlying chronic pain in deep tissues like the masticatory muscles in TMD [122 7].

Neuronal hyperactivity may be down-regulated by GABAergic inhibition [116]. The pain information transmitted from the periphery to the brain, besides being determined by the excitatory input, is also modulated by inhibitory input in the spinal cord and subnucleus caudalis, or descending from the brain. Peripheral tissue injury may also reduce the amount of inhibitory control over dorsal horn neurons. In persistent pain states, the inhibitory neurotransmitter GABA is reduced along with GABA receptors and opioids receptors, which usually exist pre-synaptically in primary afferent fibers and post-synaptically in dorsal horn [112 114] and subnucleus caudalis neurons. Loss of GABA inhibition is characteristic of persistent pain [114 116]. In addition, the expression of cholycystokinin, an endogenous inhibitor of opiate receptors is up-regulated in persistent centrally mediated pain [112].

This loss of inhibition would induce an increased input in the spinothalamic tract and hence to the higher centers in the brain [117]. The disinhibition net effect resulting from these processes may induce spontaneous firing of dorsal horn cells or exaggerated responses of these cells to primary afferent input [112]. When this process is added to the ascending central sensitization, there is a persistent pain perception.

1.5.1.3 CLINICAL CHARACTERISTICS OF CMM

The diagnosis of CMM is based on a detailed clinical history and on the clinical signs and symptoms presented by patients. Since CNS effects might constitute a significant part of the pain

in CMM [8,71] there are no specific radiographic, histopathologic or laboratory tests to diagnose such condition.

CMM often presents with symptoms of an inflammatory condition of the masticatory muscles and therefore is confounded with myositis. However, the typical signs of inflammation (e.g. redness, swelling, and heat) are not present [3]. This is histologically supported by different biopsy studies that found no evidence of inflammation in samples of muscle tissue with chronic pain [93,94].

The main feature of CMM is the continuity of the pain. Many muscle pain disorders are recurrent, meaning that they manifest with episodes of pain with intermediate periods of absolute pain relief. It is characteristic of patients with CMM to present constant, aching myogenous pain [3,41]. The pain is present at rest and increases with mandibular function.

The IASP indicates that pain should be considered chronic when is present for three to six months [40]. For this reason, the duration of the pain problem is a significant clinical feature of CMM. The constant pain, with no periods of total remission, is often present for long periods that can range from four weeks to several months [3].

Patients experiencing CMM present with dysfunction of the masticatory muscles [41]. This is translated to a significant decrease in the velocity and range of mandibular movement [3]. The fact that the normal range of movement cannot be achieved is due to the pain itself and not to structural musculoskeletal causes [3].

Since that pain in CMM is constant, patients experiencing this condition will report myogenous pain even when the masticatory muscles are at rest [41]. Pain at rest is a key clinical feature to direct our diagnosis to CMM and it is likely caused by sensitization of the muscle nociceptors by algogenic substances [3]. In CMM there is always a constant baseline of pain, which can be significantly increased with mandibular function. Activities such as mastication, talking, laughing, sneezing, among others can significantly increase the pain level in the masticatory muscles.

CMM is also characterised clinically by local muscle tenderness [3 41]. Extraoral palpation of the masticatory muscles will be positive in these patients. This means that palpation to the muscles will significantly increase the constant pain level in the affected muscles. On occasions, the pain can be referred to other unaffected areas of the head upon extraoral palpation due to the presence of myofascial trigger points. It is not uncommon to encounter CMM concomitantly with regional myofascial pain [3 41]. Although the pathophysiology of myofascial pain is still not fully understood, it is suggested that, as in CMM, there is important CNS influence [70 131]. For this reason patients with CMM may also complain of having different referral pain patterns in the head and neck area.

Another important clinical characteristic present in CMM is patients reporting a feeling of muscle tightness [3]. Contracture of the masticatory muscles is common in patients with CMM because in order to reduce their pain, they will limit their mouth opening [3]. This refers to a painless shortening of the functional length of the muscle. A state of contracture will resist any sudden attempt to lengthen the muscle.

1.5.1.4 PSYCHO-SOCIAL IMPLICATIONS OF CMM

The relationship between CMM as a TMD and psychosocial factors is widely documented in the literature [2 7 41 132]. This relationship has been described in a bi-directional way. It has been reported that psychosocial factors may predispose TMD [132] but on the other hand, chronic TMD can have a significant impact in the psychosocial aspect of patients [41].

Chronic pain is more often related with psychological and social factors than acute pain. However, chronicity of the pain does not imply necessary psychopathology, so long as the emotional and behavioural correlates of the pain experience remain proportionate to the reality of the patient's organic disease and anticipated distress [2]. When chronic pain has associated psychosocial and behavioural impairment, it is defined as "Chronic Pain Syndrome" [2]. In this case, chronic pain can be perceived more as suffering than a sensory experience, as occurs in acute pain.

Stress is a psychological factor that has been associated to the development of chronic pain. It is suggested that stress caused by the environment, intrapsychic tensions, or both results in neurophysiologic processes that produce pain and other symptoms [7].

Pain and psychological factors, including mood, temperament and affective disorders, can interact dynamically in five different ways [133]: psychological factors predisposing pain, psychological factors precipitating pain, psychological factors exacerbating pain, psychological factors as a consequence of pain and psychological factors perpetuating pain.

A predisposing factor is typically an inherent attribute that generates a tendency to a particular outcome. Psychological factors as predisposing conditions in pain mainly consist of different types of personality traits, which may increase the likelihood of a physical perception problem [133]. On the other hand, a precipitating factor is a relatively immediate trigger of a response. In the psychosomatics of pain, psychological conditions, such as anxiety can operate as a proximal trigger to pain. Anxiety leads to hypervigilance, arousal, and judgmental bias. These increase the likelihood that a stimulus is perceived as painful [133]. Psychological factors can be also considered as exacerbating, when they aggravate rather than initiate the pain response. Interpersonal conflict and non-pain related circumstances associated to affective distress and anger can still augment pain [133]. Psychological factors are known to produce endocrine changes along with sympathetic nervous system arousal that may have an intensifying effect on persistent pain. It is important to acknowledge that negative influence of psychological factors not only can trigger pain but also come back and aggravate it, creating a vicious cycle in which both entities are intimately associated [133].

In many cases, negative psychological factors can be a consequence of chronic pain. This implies a causal link between the pain as a precursor, and psychological factors as a consequence. At this stage, distress is more than just the unpleasantness that is found in any type of pain. It becomes differentiated by more complex emotions, such as fear, guilt and shame [133]. The particular emotion can be stretched out into an enduring mood, and in severe cases, an affective disorder. Depression has predominantly received attention in pain research, in comparison to anxiety and anger [133]. This research indicates that depression has a greater role as a consequence rather than a cause of pain [133]. Besides depression, chronic pain dysfunction shows an increasing relationship

with unemployment rate, a pain disability scale score, and interference with family and social activities and frequent pain-related health care visits [41]. This may lead to dysfunctional chronic pain, which is defined as a severe and persisting pain accompanied by seven or more days in which the patient is unable to carry out usual activities because of pain [41].

Finally, psychological factors can also act as perpetuating factors of chronic pain, meaning that it can extend pain in time rather than to amplify its intensity [133]. Pain behaviours such as complaining and listlessness may be reinforced by consequences that are pleasing to the patient, such as attention and solicitude from the social environment, that are positive in terms of the affect generated [133]. These types of pain behaviours may result in a sick role expressed by perpetual suffering and disability, when actually the patient is obtaining positive gain from this condition. In extreme cases, this may lead to clinical disorders, such as fictitious or malingering disorders [133].

In the particular case of chronic TMD and CMM, anxiety and depression have been significantly associated to the mantainance of these and other orofacial pain conditions [5 134]. Somatization has been highly associated to the aetiology and pathophysiology of chronic muscular facial pain in TMD patients and has been found in a significant portion of this patient population [15 17-19 80]. This psychiatric disorder has been considered a strong predictor for an increase of pain dispersion in patients with chronic TMD [17]. Kinney et al. [15] reported that approximately 50% of people seeking treatment for TMD in a facial pain clinic were diagnosed with somatoform pain and somatization. In patients with CMM stress is a very important psychological factor that originates and maintains physical responses in the CNS [30], which highly influences musculoskeletal pain responses [76]

1.5.1.5 IMPACT OF CMM ON SLEEP ARCHITECTURE

Sleep is a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment. In unusual circumstances, behaviours such as sleepwalking, sleep-talking and tooth grinding can occur during sleep [135]. Sleep architecture can be divided in two periods: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is divided into four different sub-stages, I, II, III and IV, reflecting a successive "depth" of sleep. Stages I and II are considered to be the light sleep stages. Stages III and IV are the deep sleep stages and are associated with the "sleep recovery effect" [135] [136]. REM sleep covers 20% to 25% of total sleep time. It is characterised by low-voltage cortical electroencephalogram (EEG) activity, phasic eye movements [137] and profound muscle relaxation [136] [137]. This period is dominant during the early morning hours, in the last third of the total sleep cycle [136].

Pain has been often linked to complaints of sleep disturbances and fatigue [138-141]. In acute pain, pain precedes complaints of poor sleep in 50% to 90% of cases [142] [143]. However, in chronic pain there is a bi-directional relationship with sleep disturbances, since a low quality of sleep may induce increased pain, and high pain levels may interfere with regular sleep quality [144] [145], becoming a vicious cycle.

In patients with chronic orofacial pain problems, such as CMM there is reduction of sleep stages III and IV [146], which are considered to be the restorative stages. In such patients, sleep is often more fragmented in comparison to healthy subjects [147]. Fragmented sleep is characterised by frequent micro-arousals that can last from 3 to 10 seconds, with associated transient heart, brain and

muscle activation. There are also frequent awakenings, which are activations that last 10 to 15 seconds, with possible associated consciousness. Shifts from deeper to lighter sleep stages are also frequently accompanied by body movements [146] [147]. All these changes may occur in clusters every 20 to 40 seconds, accompanied by changes in cortical waves, heart rate and muscle tone [147]. Reduction of sleep stages 3 and 4 and the frequent occurrence of these fragmentation changes during sleep, lead to non-refreshing sleep [147].

Poor sleep quality can lead to secondary daytime fatigue, lack of concentration, memory dysfunction, and increased of motor vehicle and work-related accidents. This may explain the interrelationship between chronic pain and irritability [147]. It is important to remember that anxiety and chronic pain are interrelated. Anxiety is an important factor in insomnia and poor sleep, therefore patients with chronic pain are at high risk for insomnia [142] [143]. This may help to explain the cyclic interaction between chronic pain, sleep and psychological factors.

1.5.1.6 **FIBROMYALGIA AND CMM: AN OVERLAP**

Fibromyalgia is characterised as chronic widespread pain and the presence of tender points, often accompanied by the presence of non-specific symptoms like fatigue, depressive mood and decreased sleep quality [74]. It is considered to be a multifactorial problem since neuroendocrine perturbations, sleep disturbances, health beliefs, mood disorders and physical deconditioning play a significant role in the persistence and perception of pain [74]. The quality of life of these patients is considerably disturbed leading to serious functional and work disabilities.

Fibromyalgia is one of the most common medical conditions seen by rheumatologists. It affects up to 2% of the general population and can start at any age, being at least 7 times more prevalent in women than in men [66]. In many cases CMM may be part of fibromyalgia syndrome, as these patients experience pain all over the body muscles. It is reported that 18.4% of patients with TMD also have fibromyalgia [148] and 75% of patients with fibromyalgia present TMD of muscular origin [148 149]. This indicates a significant overlap in the prevalence of both conditions.

Like CMM, the pathophysiology of fibromyalgia is not completely elucidated. Central mediation of the pain has been proposed, involving an aberrant sensitization of pain at the spinal cord level, where NMDA receptors appear to be hyper-excitable [74] and also reduced function of the descending inhibition system [74]. However, peripheral and psychological factors have also been implicated with the onset and mantainance of this condition [69].

Clinically, fibromyalgia presents many similarities to CMM: chronic musculoskeletal pain, muscle tender points, morning stiffness and fatigue without specific laboratory findings [150 7 151 152]. Fibromyalgia is considered soft-tissue rheumatism. Although pain is felt in the joints, fibromyalgia is a non-articular disorder because the pain originates from the ligaments and muscle insertions [74]. Other clinical symptoms present in fibromyalgia that are common with CMM include psychological conditions such as depression, anxiety, concentration difficulties and non-restorative sleep [74 153].

1.5.1.5 GENERAL OVERVIEW OF TREATMENT AND MANAGEMENT MODALITIES OF CMM

The management of CMM involves more than one modality. Unfortunately, there is no magic bullet to treat chronic pain problems, and the management is rather multidisciplinary. Since these problems are multifactorial in origin, they need to be approached from different perspectives, in order to obtain the best results.

Occlusal treatments and physical therapy modalities in CMM

Splint appliances are widely used to reduce masticatory muscle pain. The effectiveness of splints in reducing TMD symptoms has been reported to vary between 70% and 90% [154]. Splint appliances have therapeutic value in reducing masticatory pain of myogenous origin, such as myofascial pain [155 156]. It is reported in several studies that splint appliances provide masticatory muscle pain reduction, ranging from 14% to 63% and complete pain resolution from 14% to 59% of cases [157-161]. Stabilisation splint appliances are effective in reducing facial pain caused by TMD, but do not reduce the clenching and grinding activity of sleep bruxism [162 163]. The mechanism of action of these appliances has not been fully elucidated and it may be possibly mediated through a placebo effect [164].

Therapies involving changes in the occlusion with simple occlusal adjustments, prosthodontics or orthodontics work are not supported in the literature and are not advised for managing TMD symptoms [2 165]. Experimental evidence has revealed that occlusal adjustment therapies are not effective in treating TMD, SB or headaches [166].

Physical therapy modalities are used to improve function and also ass a pain palliative approach in CMM. These modalities include thermotherapy, coolant therapy, phonophoresis, inotophoresis, electrogalvanic stimulation therapy, acupuncture and transcutaneal electrical nerve stimulation (TENS). These techniques promote an increase of blood flow in the area, stimulation to nerve and muscle fibers, release of endogenous opioids and muscle relaxation leading to a local decrease of the pain sensation [3]. Manual techniques such as soft tissue mobilization, TMJ distraction, isotonic and resistance exercises are also utilized to decrease pain levels and improve function that has been decreased by the presence of pain. The role of physical therapy in this condition is mainly palliative and complementary to the rest of the multidisciplinary treatment plan [3].

Pharmacological management of CMM

Regarding pharmacological management, the literature does not provide evidence-based support for a specific TMD treatment [167]. Traditionally, clinical decisions have been based on past clinical experience, training, practice traditions and the opinion of recognized authorities. The scientific support for these treatments has been questioned and more randomized controlled trials (RCT) are required to obtain definitive conclusions in regards to the analgesic efficacy of medications on chronic TMD pain.

In clinical practice, the management of CMM includes five groups of medications: 1) non-steroidal anti-inflammatory drugs (NSAIDs); and acetaminophen; 2) muscle relaxants; 3) antidepressants; 4) antiepileptic agents; and 5) opioids.

Acetaminophen and aspirin are considered simple analgesics for mild to moderate pain. They are of limited efficacy in managing chronic pain and more RCTs are required to support their use in this area. However, they are commonly used in clinical practice for break through pain and episodic pain increments. NSAIDs, such as ibuprofen, naproxen, diclofenac, ketorolac, among others, are generally well tolerated and are mainly indicated for musculoskeletal problems [168] and chronic inflammatory conditions [169]. However, when administered for prolonged periods, these medications can result in undesirable gastrointestinal and renal side effects, therefore their use is recommended for short trials in patients where pain has an apparent inflammatory component [170]. These medications have their analgesic effect by inhibiting the production of cyclo-oxigenase and therefore, prostaglandins. Since inflammation does not appear to be the basis of chronic myogenous pain [2 93 94], NSAIDs appear to have little effect on this condition [171].

Muscle relaxants are widely used in clinical practice as palliative agents for TMD of muscular origin [172]. These medications are often administered to patients with chronic orofacial pain to prevent or alleviate the increased muscle activity related to TMD pain [132]. Most muscle relaxants have a central effect that sedates the patients, rather than acting directly on the muscle tissue. This may be the main explanation for the positive response of some patients [3 169]. Cyclobenzaprine has been demonstrated to be effective in some chronic musculoskeletal problems such as pain in the lumbar and cervical regions, which is suggestive of its efficacy for pain palliation in the masticatory muscles [170]. Benzodiazepines are also frequently utilized for muscle relaxation but they decrease muscle tone only at doses that produce CNS depression [170]. Therefore its clinical use is limited to short trials when utilized as palliative agents for masticatory muscle pain.

The use of tricyclic antidepressants (TCA) is documented in the literature for chronic orofacial pain [173 33 35 36 172 174-176] and chronic musculoskeletal pain conditions [177-181]. Unfortunately, there are no RTC addressing their analgesic activity specifically on CMM. These medications act centrally by increasing the availability of certain neurotransmitters (noradrenaline or serotonin) in the synaptic cleft of central nerve terminals [168 170 176]. The most commonly used agents are amitriptyline and its metabolite nortriptyline. These medications also appear to be effective in improving sleep quality [178 182], which is often beneficial for chronic pain patients. Although TCAs were initially developed to treat depression, it is reported that its analgesic effect is independent of the antidepressant action. Analgesic doses of amitriptyline are usually low, ranging from 10mg to 50mg [178], while much higher doses are usually required to produce an antidepressant effect [33]. The most common side effects of these medications include drowsiness, dry mouth and weight increase [183].

Antiepileptic agents are also frequently used to treat chronic orofacial pain conditions. However, these medications are usually utilized to treat problems of neuropathic origin [37 121 183 184], which cause an overexcitement of the whole system, by central and peripheral mechanisms. Antiepileptic agents act peripherally and centrally as membrane stabilisers since they block ion channels present in the neuron cell membranes to decrease the firing of pain information to the brain [121 185]. Besides their use in neuropathic pain, it is reported in the literature that antiepileptic drugs improve sleep quality [186]. To date, there are no RCT evaluating the analgesic effect of any of these agents specifically on CMM, and their use for this condition is mainly based on clinical experience. Research with high levels of evidence is required to determine the analgesic effect of these drugs on centrally mediated chronic musculoskeletal pain.

Opioid drugs mimic endogenous opioids and activate opioid receptors to produce analgesia. However, since these drugs are not selective for those receptors that effect analgesia, other side effects are manifested. These include respiratory depression, sedation and euphoria [183]. In addition, tolerance and a low risk of addiction are associated to these agents [168]. For these reasons, the use of opioids in clinical practice to manage CMM is considered when other pharmacological and non-pharmacological treatment options result in poor pain control.

Psychological therapies most commonly used in CMM

Chronic TMD are related to certain emotional states [3]. In many cases, psychological factors and chronic pain are highly interrelated becoming a part of the same vicious cycle. When required, it is important to start psychological interventions during the development of chronic painn to avoid the establishment of poor pain behaviour.

When high levels of emotional stress are suspected, treatment is directed toward the reduction of these levels. Relaxation techniques have been demonstrated to be effective to reduce stress levels in chronic TMD [3]. The rationale for relaxation therapy lies in the assumption that pain is a stressor and increases muscle tension, causing a vicious cycle [168]. Patients also feel that this method gives them control over the pain. These techniques include breathing exercises and meditation. They appear most effective when provided through frequent visits to well-trained therapists in order to help and encourage proper relaxation habits. These techniques are considered as part of cognitive behaviour therapy, which has been systematically reviewed [168].

Biofeedback therapy is used to demonstrate to the patient that stress and pain can have on a variety of physiological functions. With biofeedback, patients are taught how to alter these functions utilising relaxation techniques [168]. Hypnosis therapy is also utilized in chronic pain. This approach attempts to decrease sensory and proprioceptive input, to lower arousals and to increase feeling of calm and well being [168]. The literature exploring the efficacy of hypnosis in chronic pain management has been broadly supportive [187], although the mechanism of action is controversial. Counselling and cognitive behaviour therapies are also commonly used approaches in chronic pain. These treatment modalities are focused to provide patients with coping skills. Such coping skills should increase tolerance to pain, improve mood control to alter feelings of anger and anxiety, encourage positive thinking, and help patients to have their own role in the treatment [168].

In those cases in which CMM is accompanied by depression, it is very important that patients are not only treated for their pain but also for their depression. Depression may modify pain perception and increases patients' susceptibility to somatic disorders [168]. It is well documented that patients with depression and physical illness respond successfully to antidepressant therapy [188]. Besides pharmacotherapy, depression related to pain can be addressed with cognitive behaviour therapy, patient education [168] and support groups [168 189 190]

1.5.2 GABAPENTIN AND CMM

1.5.2.1 GENERAL OVERVIEW OF THE USE OF ANTIEPILEPTIC AGENTS IN OROFACIAL PAIN

Antiepileptic agents are primarily used in the prevention and treatment of seizures. However, their use in health care is not limited to epilepsy. They are also widely used to treat different types of chronic pain conditions [37 121 183 184], such as trigeminal neuralgia, post-herpetic neuralgia, diabetic neuropathy, central pain after stroke, phantom limb pain, TMD, and headache prophylaxis [183].

In orofacial pain, antiepileptic agents are widely used for the management of chronic conditions, mainly of neuropathic origin. Carbamezapine is considered the first choice drug in the treatment of trigeminal neuralgia [37 191 192]. Phenytoin was also considered as a second option in the treatment of trigeminal neuralgia when carbamezapine was not effective. Oxcarbazepine, a newer antiepileptic derived from carbamezapine, has shown to be effective in trigeminal neuralgia with a cleaner side effects profile [193]. Lamotrigine is a newer anticonvulsant, which has been found to be helpful in trigeminal neuralgia as an add-on therapy [194] and has been suggested as a possible option for prevention of migraine with aura [195]. Gabapentin has been also used for this condition with fewer side effects [37]. This drug has also shown to be effective in the prevention of migraine headaches [23] and is used in clinical practice for treatment of deafferentation dental pain. Clonazepam, a member of the benzodiazepine family, has been reported to be beneficial in TMD, in comparison to placebo [183]. Topiramate is now gaining popularity as an effective agent for migraine prophylaxis and cluster headache as is supported in the literature [196 197-200 201 202].

The analgesic mechanism of antiepileptic agents in orofacial pain varies depending on the pharmacological target in which they exert their action. Phenytoin, carbamezapine and oxcarbazepine have membrane stabilizing-effect by blocking sodium channels [37] [184] [193]. Valproic acid has been shown to increase the amount of GABA in the brain, enhancing the activity of glutamic acid decarboxylase and inhibiting GABA degradation enzymes [184]. Although gabapentin does not act on GABA receptors, a global increase of GABA levels after administration of gabapentin has been documented. Recent studies suggest that gabapentin inhibit neurotransmitter release by blocking calcium channels [184] [203] [204] . Lamotrigine probably acts by stabilizing a slow inactivated confirmation of a sodium channel and suppressing the release of glutamate from presynaptic neurons [184]. Topiramate presents several mechanisms of action including modulation of sodium channels, potentiation of GABA-ergic inhibition, blockage of excitatory glutamate activity and also blocking calcium channels [184]. Benzodiazepines are GABA agonists that have analgesic properties in the spinal cord and brainstem of animal models. It has been reported that clonazepan can normalize significantly the nociceptive threshold in rats with chronic constriction injury to the sciatic nerve [205].

1.5.2.2 CLINICAL EFFICACY AND USE OF GABAPENTIN IN OROFACIAL PAIN

Gabapentin is approved by the FDA for treatment of epilepsy and post-herpetic neuralgia. However, this medication has been used and tested for many other conditions in clinical practice and research studies [183] [206]. In orofacial pain, gabapentin is used as a secondary option for the management of trigeminal neuralgia, for migraine and chronic headache prophylaxis, chronic

masticatory muscle pain, dental deafferentation pain and atypical facial pain. Unfortunately, there is a lack of well-controlled clinical trials to give sufficient scientific support to these uses in clinical practice. More RCT testing gabapentin for different types of orofacial pain conditions are required in order to draw definitive conclusions about its application in orofacial pain.

To date, the literature presents few studies in which gabapentin has been tested for orofacial pain conditions. There are three open label studies evaluating its analgesic efficacy on trigeminal neuralgia. A case series by Merren et al [207] tested gabapentin on seven patients for 19 months with a dose of 1500mg. Five patients reported complete pain relief, whereas one patient partial relief and one other patient did not experience any pain relief at all. Valzania et al [208] tested doses of 1100 mg/day on seven trigeminal neuralgia patients. This study lasted for three months, during which only one patient reported absolute pain relief. Out of the remaining six patients, three reported partial relief and three no relief. An open study by Khan et al [209] reported partial and complete pain relief after taking gabapentin for two weeks in multiple sclerosis (MS) patients with trigeminal neuralgia. Two case reports by Sist et al [210] [211] tested gabapentin in patients with trigeminal neuralgia and neuropathic facial pain with doses ranging from 900mg to 2400mg per day. Gabapentin was effective in absolute and partial relief of symptoms of trigeminal neuralgia. It was also effective in diminishing steady burning pain as well as lancinating pain and allodynia. Other case report by Solaro et al [212] reported pain control in ten out of eleven multiple sclerosis (MS) patients with trigeminal neuralgia. No side effects were reported and the treatment dose was 1200mg per day, utilized as an add-on therapy combined with either lamotrigine or carbamezapine.

Gabapentin has been also evaluated for migraine prophylaxis. One case series study conducted by Merren et al [207] demonstrated a significant reduction of attack frequency in more than 80% of the patients who completed the trial. Cerbo et al [213] conducted a study testing gabapentin on fourteen migraine patients, of which three reported total relief, eight partial relief and five no relief. Two RCT have been performed testing gabapentin as a migraine prophylactic agent. Mathew et al [23] found that 46.4% of patients receiving gabapentin 2400mg per day showed at least a 50% of efficacy in comparison to the placebo group. Di Trapani et al [22] reported that gabapentin reduces migraine frequency in 36% of patients treated. There is also a RCT evaluating the prophylactic effect of gabapentin on chronic daily headache by Spira et al [214]. This study showed that gabapentin was superior to placebo in terms of reduction of headache frequency, severity and disability. In addition there is an open study conducted by Fragoso and Carrazana [215] evaluating gabapentin also on chronic daily headache, in which 19% of patients reported subjectively an "excellent" response to treatment; 47.6% reported it as "good", 19% as "fair" and 14.4% as "poor".

Case reports have been published reporting the efficacy of gabapentin on other orofacial pain conditions. Lucier et al [216] reported facial neuritis pain relief with gabapentin doses ranging from 100 to 300mg per day after two days of treatment. Schachter et al [21] reported significant pain control with 900-1800mg per day for three to twelve months in patients with facial pain refractory to other treatments. Childs et al [217] reported dramatic pain relief after gabapentin was administered to a patient with pain secondary to neurovascular compression of the trigeminal and glossopharyngeal nerve. Schachter et al [218] reported a complete resolution of post-stroke pain in the left periorbital and maxillary regions at the beginning of gabapentin treatment. However, the pain returned with less frequency than before gabapentin treatment. In addition to these reports,

Moretti et al [219] reported a four-year follow up case of gabapentin treatment for glossopharyngeal neuralgia. In this case, the patient responded absolutely to gabapentin with no complaints of side effects and a reduction of pain in the second reminiscence cluster of the crisis.

It is important to know what level of evidence based medicine (EBM) is available in the current literature regarding the use of gabapentin in orofacial pain. This would help to determine further research direction in the area. EBM has five main levels ranging from level 1, being the highest to level 5, being the lowest. This ranking depends on the methodology and study design implemented. Table 1.1 shows the different levels of EBM for treatment approaches established by the group of Phillips et al [220]. Table 1.2 classifies the above-cited studies into their EBM levels.

EBM LEVEL	THERAPY PREVENTION, ETIOLOGY/ HARM
1a	Systematic review of randomized controlled studies (RCT)
1b	Individual RCT (with narrow confidence interval)
2a	Systematic review of cohort studies
2b	Individual cohort studies (including low-quality RCT; eg,< 80% follow up)
2c	"Outcomes" research; ecological studies
3a	Systematic review of case control studies
3b	Individual cross-sectional and case control study
4	Case control / cross sectional studies (and poor- quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "proof of principle study"

Table 1.1: Levels of EBM for therapy / prevention / aetiology / harm [220].

Authors	Type of pain evaluated	Study design	Evidence level	Conclusion
Schachter 1996	Post-stroke pain	Case report: one case	5	Temporary pain control
Cerbo et al 1997	Migraine prophylaxis	Open label study	4	Total relief in 21.42% of patients; partial relief in 57.14% and no relief in 35%.
Lucier et al 1997	Facial neuritis	Case report	5	Pain relief after 2 days of treatment
Sist et al 1997	Trigeminal neuralgia	Cases report: 2 cases	5	Partial and absolute pain relief
Sist et al 1997	Neuropathic pain in face and head	Cases report: ten cases	5	Partial and absolute pain relief
Schachter 1997	Intractable facial pain of neuropathic and neurovascular origin	Case reports: 9 cases	5	Pain control clinically significant with doses ranging from 900 to 1800mg/day
Khan et al 1998	MS patients with trigeminal neuralgia	Open label	4	Partial and complete relief of pain
Merren et al 1998	Migraine headaches (MH) & trigeminal neuralgia (TN)	Case series	4	**MH**: Effective in 80% of patients. **TN:** Complete control in 5 out of 7 patients
Valzania et al 1998	Trigeminal neuralgia	Open label	4	Effective in 83% of patients
Childs et al 2000	Pain secondary to neurovascular compression of the trigeminal and glossopharyngeal nerve	Case report: one case	5	Dramatic and clinically significant pain relief.
Di Trapani et al 2000	Migraine prophylaxis	RCT	1b	Effective in 36% of patients
Fragoso & Carrazana 2000	Chronic daily headache	Open label	4	"Excellent" in 19% of patients
Solaro et al 2000	MS patients with trigeminal neuralgia	Case report: 11 cases	5	Effective in 10 out of 11 patients
Mathew et al 2001	Migraine prophylaxis	RCT	1b	46% of patients showed at least 50% of relief
Moretti et al 2002	Glossopharyngeal neuralgia	Case report: one case	5	Absolute but temporary pain relief
Spira et al 2003	Chronic daily headache	RCT	1b	Gabapentin is significantly superior to placebo in reducing frequency, severity and disability

Table 1.2 - Current evidence for the use of gabapentin in orofacial pain: Studies and clinical reports evaluating the efficacy of gabapentin on different types of orofacial pain conditions.

To date there are no clinical trials in the literature evaluating the analgesic efficacy of gabapentin specifically on chronic musculoskeletal pain. From an orofacial pain perspective, gabapentin has been used in clinical practice to manage chronic TMD of myogenous origin. Unfortunately, no clinical trials are available to support this practice. There is one retrospective study by Gustorff et al [39] that evaluated the analgesic effect of gabapentin on chronic intractable pain of diverse origins. Interestingly, 35% of patients with intractable musculoskeletal pain responded to gabapentin treatment. Although this study is not specific for the orofacial pain region, its results are suggestive of a possible analgesic action on chronic pain in the facial and head muscles.

1.5.2.3 GABAPENTIN: PROPOSED ANALGESIC MECHANISMS OF ACTION

Gabapentin, 1-(aminomethyl) cyclohexane-acetic acid, is a cyclic γ-aminobutyric acid (GABA) analog. Gabapentin is a γ-amino acid with an attached cyclohexabe ring [221]. Gabapentin was originally developed to imitate GABA, but it is inactive in GABA receptors [20 185]. Gabapentin can resemble the structure of the L-form of large neutral aminoacids that are substrates for a saturable, sodium-independent L-aminoacid transport system [20 221]. Gabapentin has been proved to mediate its effects at central [20 222 223], as well as peripheral sites [224 225 226] and suppresses pain from inflammatory [227] and neuropathic mechanisms [226 228].

The mechanism by which this drug produces its effect has not been established, but several hypothetical mechanisms have been proposed. These include body membrane crossing mediated by a specific amino acid transport system (system L); increase of GABA concentration in brain; high binding affinity with voltage sensitive Ca+ channels; sodium channel blockade; reduction of

the release of certain neurotransmitters; and the increase of serotonin in blood [20 185 221 229]. It is also important to point out, that the anticonvulsant and analgesic effects of this drug are supposed to have different mechanism of action, since the analgesic activity occurs more rapidly than the antiepileptic action, once gabapentin is administrated [20].

The ability of gabapentin to cross barriers within the body is very low, but as any other amino acid, it is a substrate of the system L transporter of gut [230]. This transport system facilitates gabapentin molecules to cross barriers within the human body [231]. There is also another little transport component related to passive diffusion that helps with the barrier crossing [20]. These transportation properties allow gabapentin to accumulate in higher concentrations in brain cytosol [20]. High densities of gabapentin binding are localized in the superficial neocortex, cerebellar cortex, and dentritic regions of hypothalamus [232].

GABA is an important inhibitory neurotransmitter in the brain that decreases neural membrane action potentials. When synapses of GABA are impaired, seizures occur. This is why several GABA enhancing drugs prevent epilepsy episodes [20]. The similar chemical structures of gabapentin and GABA, may suggest a functional relationship, but they do not act in the same way, because it has been shown that gabapentin does not interact with GABA receptors [20]. It has been reported that gabapentin modulates the activity of glutamic acid decarboxylase (GAD), and therefore it might increase indirectly GABA levels in the brain tissues [20 185 232]. In addition to this increase of GABA levels, it has been suggested that gabapentin also suppresses glutamate in the trigeminal nucleus and thalamus. Both, high GABA levels and glutamate suppression, produce a decrease of pain messages ascending from the trigeminal nucleus and thalamus to the cortex [20 232]

The release of neurotransmitters from neuronal tissues can be mediated by calcium channels mechanisms [20 121 185 229]. It has been demonstrated that gabapentin reduces membrane calcium currents [233]. In centrally mediated pain, ongoing membrane depolarization leads to an increased action potential, which results in activation of calcium channels to release neurotransmitters that mediate pain information. The release of these neurotransmitters would result in increased neuronal hyperexcitability promoting chronic pain states [234]. It has been suggested that gabapentin binds to calcium channels involved with pre and post-synaptic processing of sensory nociceptive information, where it is assumed to act as an antagonist [233 235]. This would decrease calcium currents [233] and prevent the ongoing neuronal hyperexcitability in persistent pain states.

L-type calcium channels consist of a α1 subunit, which forms the Ca^{2+} conducting pore, and three accessory subunits: α2δ, β and γ. It has been shown that Gabapentin binds to the α2δ subunit of the L-type calcium channels in brain and skeletal muscle membranes [203 204]. The α2δ subunit appears to be important for the calcium channel assembly [203 204]. It is not confirmed yet if the gabapentin binding site to this subunit is extra or intercellular [203]. It has been suggested that Gabapentin interaction with calcium channel subunit induces the disruption of the association of α2δ subunit with the channel complex [235]. In addition, it has been reported that gabapentin promotes a long-term down-regulation membrane expression of N-type calcium channels [235], which demonstrates that this drug not only acts on L-type calcium channels. Since this subunit type appears to be common to all voltage-dependent calcium channels, it is suggested that gabapentin can exert its blocking action in more than one type of neuronal calcium channels [203].

Calcium channels are multi-subunit complexes found not only in the brain but also in peripheral tissues such as skeletal muscle, heart and lungs [20]. The skeletal muscle L-type calcium channel plays a critical role in excitation-contraction of the myotubes in the muscle [225]. Its activation initiates three main functions: charge movement, calcium release and calcium currents. Interestingly, a recent study [225] has shown that gabapentin binds to the α2δ subunit of these calcium channels in the skeletal muscle, causing a dissociation of the channel functions.

It has also been reported that gabapentin acts on sodium channels, causing their blockade, which decreases the excitability of nerve membranes and transmission of nociceptive sensations. In other words, it decreases the action potential [221 232]. However, further research in this area is required to draw definitive conclusions on this possible mechanism of action.

The analgesic effect of gabapentin is mostly related with its action on certain neurotransmitters, since it causes a significant decrease in the release of noradrenalin, dopamine and serotonin [20 236]. There is a reduction of monoamine release that may be related to an action on Ca+ channels or to changes in monoamine metabolism. This action is not directly related with the anticonvulsant effect, but it might have influence on behavioural effects and analgesia [20]. It has been reported that because of the fact that gabapentin can block thermal and mechanical hyperalgesia, it may work from a spinal level, specifically in dorsal horns [20 229]. In addition, it has been reported that gabapentin induces inhibition of the branched-chain amino-acid aminotransferase, which is an important enzyme in the metabolic pathway of glutamate. This suggests that gabapentin also reduces significantly the sysnthesis of glutamate in the brain, by acting on this enzyme [237].

Recent studies suggest that gabapentin may also act on a presynaptic level. For instance, it has been suggested that gabapentin downregulates NMDA currents enhancement [238] by increasing the activity of the inhibitory GABA-ergic neurons [239]. This results from an increase in the affinity of glycine for NMDA receptors by gabapentin [238]. In addition to its possible action on NMDA currents, it has been reported to modulate the release of substance P and calcitonin gene-related peptide only under conditions associated with significant inflammation-induced sensitization of the substantia gelatinosa [240]. Although it was thought that gabapentin does not have analgesic action on acute pain situations [227 241], it may play a role in presynaptic transmitter release during pathological conditions such as chronic inflammation [240 242]. In addition, recent RCTs evaluating the effect of gabapentin on postoperative pain have been performed and systematically reviewed [243]. Their results show an analgesic postoperative effect of gabapentin when administered as a protective premedication before surgery, as it reduces hyperalgesia as a clinical sign of central sensitization secondary to surgery [243 244]. More clinical trials are required in order to make definitive conclusions regarding the analgesic role that gabapentin may have in acute pain.

The analgesic mechanism of action of gabapentin is not yet fully elucidated. The main proposed mechanisms of action appear to be calcium channel blockage, and indirect GABA increase in the brain. More research is required in order to confirm the rest of the proposed mechanism through which gabapentin exerts its analgesic effect in chronic pain states.

1.5.2.4 EFFECT OF GABAPENTIN ON SLEEP ARCHITECTURE

As mentioned before, patients with chronic muscle pain often present poor sleep quality. In many cases drugs that are used for chronic pain also help to improve sleep quality. There are studies in

the literature reporting a positive effect of gabapentin on sleep quality [186 245 246]. This is of major importance because improving the quality of sleep of chronic pain patients may help to break the sleep and pain vicious cycle.

Gabapentin increases slow-wave sleep [246 247]. This is extremely important since slow-wave sleep stages 3 and 4 are considered to be the restorative sleep stages. This was early reported in 1988 in a study conducted by Rao et al [248] and has been confirmed by recent studies [246 247]. This increase of sleep stages 3 and 4 has been attributed to an augmentation of central serotonin [248]. It is known that increased serotonin bioavailability augments stages 3 and 4 in experimental animals [249]. It is suggested that if gabapentin inhibits central serotonin release, it may also inhibit peripheral release by platelets in serum. This would make the neurotransmitter less susceptible to degradation, thus increasing its availability and eventually sleep stages 3 and 4 [248].

On the other hand, it is also reported that gabapentin decreases light sleep in stage 1 [245 246]. In addition, gabapentin increases REM sleep percentage, mean duration of REM periods, and decreases the number of awakenings [250]. A decrease in light sleep (stage 1) plus an increase of restorative sleep (stages 3 and 4) might contribute to sleep quality improvement in GBP treated patients.

These findings may support the use of gabapentin to treat different types of sleep disorders, such as restless legs syndrome (RLS) and periodic limb movement disorder during sleep (PLMS) [251]. Whether the drug's effects are due to changes in sleep quality or quantity is unknown. RLS is characterised by a desire to move the limbs, usually associated to dysesthesias/paresthesias in

the lower extremities; motor restlessness; a partial, temporary relief of the former by activity; and worsening of the symptoms in the evenings or at night [252]. RLS is a sensory-motor disorder that interferes with the patient's quality of sleep. In chronic pain patients, RLS may be another factor to decrease the sleep quality in addition to the pain. In a double blind crossover study, gabapentin was shown effective in improving sensory and motor symptoms of RLS and also sleep architecture [252]. In some cases RLS can be associated to another condition, which is PMLS [253]. These are repetitive and highly stereotyped leg movements characterized by extension of the great toe and flexion of the ankle, knee and hip [252]. In the same study [252] gabapentin proved significantly superior to placebo in decreasing PLMS in polysomnographic tests.

Sleep bruxism is now considered a parasomnia. There is no evidence reporting pain reduction in CMM by control of bruxism with gabapentin. However, there is one case report describing antidepressant-induced bruxism control with gabapentin [254].

1.5.2.5 **GABAPENTIN: PHARMACOKINETICS**

The pharmacokinetic properties of gabapentin predict a good safety profile and good bioavailability in a wide spectrum of populations. Gabapentin is rapidly absorbed after oral administration [255], with interindividual and dose-dependent variability and bioavailability [256].

Once absorbed, gabapentin reaches its peak plasma concentrations in approximately 3 hours, following single oral doses regardless of dose size or formulation [257] [258]. Steady state is achieved 1 to 2 days after beginning drug administration and is maintained during the dosing regime. Plasma

gabapentin concentrations are dose-proportional at doses of 300 to 400 every 8 hours, but are less dose-proportional above 600mg every 8 hours. Absolute bioavailability of gabapentin oral dose is approximately 60%, and this value is unchanged following multiple-dose administration [259] [258]. The presence of food does not influence significantly the bioavailability of gabapentin [257] [259] [258].

Gabapentin elimination half-life from plasma ranges from 5 to 7 hours and is unaltered by dose or following multiple dosing [259]. This drug does not bind to plasma and its elimination is only by renal clearance in an unmetabolized form without inducing or inhibiting liver enzymes [257-259]. Gabapentin elimination rate, plasma clearance and renal clearance are directly proportional to creatinine clearance [259]. Since gabapentin is not metabolized in humans, the amount of the drug recovered in urine is indicative of gabapentin bioavailability. Renal function decreases with aging, therefore, gabapentin renal clearance and elimination-rate half-life decreases proportionally [259].

Gabapentin does not appear to have significant interactions when co-administered with other drugs. There are no interactions between gabapentin and other antiepileptic agents such as phenytoin, valproic acid, carbamezapine or phenobarbital. As a result, gabapentin may be used in combination with other antiepileptic agents that are commonly used to manage pain or epilepsy without concerns for alterations of plasma concentration levels. In addition, no interactions have been noted either between gabapentin and oral contraceptives [257] [258] [259].

Co-administration of gabapentin with oral aluminium and magnesium-based anti-acids has shown to reduce gabapentin bioavailability up to 24% [257] [259]. For this reason the coadministration of gabapentin along with anti-acids is not recommended. The clinical significance of decrease in

bioavailability is not known. Hydrocodone's effectiveness is also reduced 3% to 25% when co-administered with gabapentin. However, hydrocodone appears to have an opposite effect on gabapentin since increases its effectiveness up to 14% [259]. The mechanism for this interaction is not known.

Synergistic interactions between gabapentin and morphine have been reported. A study performed by Ekhardt et al [260] demonstrated that gabapentin effectiveness increases 44% when 60mg morphine is administered 2 hours prior to a 600mg gabapentin capsule. However, the morphine pharmacokinetics does not appear to be affected. These results were supported by another trial by Caraceni et al in 1999 [261]. Since these two medications have very different mechanisms of actions, their side effect profile will not be accentuated when administered simultaneously. These findings are of great importance for the field of pain medicine, since the use of gabapentin as an adjuvant in opioid analgesia may be very helpful for chronic pain management.

Naproxen is another medication that has shown a synergistic interaction with gabapentin. Co-administration of naproxen sodium 250mg with gabapentin 125mg appears to increase gabapentin absorption up to 12% to 15%. At the same time, gabapentin does not show any effect on naproxen pharmacokinetics. These doses are lower than the therapeutic doses of both drugs [259]. This is supported by a study performed by Hurley et al [262] in which gabapentin co-administered with naproxen significantly reduced thermal hyperalgesia associated with peripheral inflammation in rats. Interestingly, their results reflected a change in the potency and not in the efficacy of the drugs. Clinically, this means that the principal advantage of this mixture is based on the administration of very low doses of each drug in combination to achieve a significant pain

reduction. This is a significant advantage to treat inflammatory pain, especially in elderly patients who are at high risk of developing renal and gastrointestinal adverse effects [262].

Finally, cimetidine 300mg appears to decrease the mean oral clearance of gabapentin by 14% and creatinine clearance by 10%. For this reason, it is assumed that cimetidine alters the renal excretion of both, gabapentin and creatinine, which is an endogenous marker of renal function. However, this decrease of excretion of gabapentin with cimetidine does not appear to be of clinical importance. The effect of gabapentin on cimetidine has not been evaluated [259].

1.5.2.6 **GABAPENTIN ADMINISTRATION AND DOSAGE**

When administering gabapentin to treat orofacial pain conditions, it should be started at a low dosage and gradually increased until pain relief occurs or adverse reactions limit their usefulness. The key element in the drug therapy to provide pain relief while avoiding as much as possible the presence of side effects, is to determine the minimum effective dose for each individual patient [37]. There is no consensus in the literature regarding the duration of therapy with gabapentin, since it varies from patient to patient. Treatment periods can range from a few weeks to several years when managing intractable pain conditions. The length of the treatment should be determined depending on the clinical observation of the patient's progress in terms of pain relief and individual tolerance of the medication [37]. If discontinuation of gabapentin is considered, gradual dose reduction is recommended in order to monitor for recurrence of pain symptoms.

Gabapentin manufacturers recommend that effective maintenance doses for epilepsy should range from 900mg to 1200mg per day for epilepsy. However, it is suggested that doses higher than 1200mg per day may have increased efficacy but may also increase the incidence of side effects [257].

Data from clinical trials suggest that when treating pain, maintenance dose tends to be higher, ranging from 600mg to 3600mg per day [38 258 263]. At these doses, gabapentin has been shown to be effective for the management of painful diabetic neuropathy, post-herpetic neuralgia and other mixed neuropathy pain syndromes [263]. When used in orofacial pain conditions, gabapentin maintenance doses have ranged from 300mg to 2400mg per day in clinical trials and case reports [21 22 196 207-210 212 214-216 218 219]. Most of these conditions are neuropathic in origin and there are no clinical trials designed specifically to evaluate at what dose gabapentin may be effective for chronic musculoskeletal pain.

Therapies with anticonvulsants such as gabapentin, should be started at low doses and gradually incremented, to reach effective analgesic action in chronic pain syndromes [37]. Due to the relatively short elimination time, gabapentin should be administered in three equal doses during the day. Gabapentin manufacturers and clinical trials suggest to start dosage with 300mg once a day for day one, 300mg twice a day in the second day (600mg/day) and 300mg three times a day in the third day to reach 900mg by this time [258 259 263]. This slow titration has been shown to be well tolerated in clinical trials [263], which may be reflected in patient compliance in clinical practice.

Once a maintenance dose of 900 to 1200mg/day is achieved, a target of a dose of 1800mg/day should be reached during the following week [263]. Clinically significant improvements in terms of pain reduction are usually seen during the second week, once a dose of 1800mg/day is achieved [263], however, this may vary from patient to patient. Once at this dosage state, it is recommended that the gabapentin should be increased up to 3600mg/day, as tolerated, to achieve better efficacy and pain control [263]. This titration protocol should be performed by 300mg every three days, keeping always the dose divided in three parts throughout the day [259].

In paediatric patients (3 to 12 years of age), the starting dose is 10-15mg/kg/day in three divided doses, achieving an effective dose in a period of 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25-35mg/kg/day administered in divided doses three times per day. In patients of ages 3 and 4, the effective dose of gabapentin is 40mg/kg/day also administered 3 times a day in divided doses. Doses up to 50mg/kg/day have been tried in clinical trials for long terms and have shown to be well tolerated [259].

Dosage should be adjusted with precaution mainly in patients with compromised renal function and in elderly patients. In elderly patients it is recommended to determine the level of renal function prior to starting gabapentin therapy. Because elderly patients are prone to have decreased renal function, care should be taken when selecting the dose. Therefore, the dose should be adjusted according to the creatinine clearance levels in these patients [257 259]. There is no need to monitor gabapentin plasma concentration levels. As there are no drug interactions with other antiepileptic agents, gabapentin can be used in combination with these drugs without concerns. Table 1.3

presents dosage guidelines for patients with renal impairment based on creatinine clearance levels [263].

Creatinine clearance (ml / min)	Dose (mg)	Total daily dose (mg/kg)
>60	400mg (3 times daily)	1200
60-30	300mg (twice daily)	600
15-30	300mg (daily)	300
<15	300mg (every other day)	150
Haemodialysis		200 – 300 *

*Loading dose of 300 to 400mg in patients starting gabapentin therapy, then 200 to 300mg after each 4 hours of haemodialysis.

Table 1.3 - Dosing according to renal function: Dosing for patients with renal impaired function based on creatinine clearance levels.

1.5.2.7 GABAPENTIN: TOLERABILITY AND SIDE EFFECTS

Traditional anticonvulsants such as carbamezapine and phenytoin, used for other neurogenic disorders can produce serious organ toxicity (i.e. hepatic, bone marrow), and therefore they are used after failure of other treatment strategies, including tricyclic antidepressants [37]. Precautions must be taken in an anticonvulsant therapy, when there is evidence of diminished bone marrow formation of blood cells, compromised renal function or abnormal levels of serum creatinine. These patients should not receive traditional anticonvulsants, although new anticonvulsants like gabapentin have been reported to be very safe.

The main advantage of gabapentin is related to the absence of serious side effects. Somnolence (20%), dizziness (18%), ataxia (13%), and fatigue (11%) are the most common side effects of

gabapentin reported in comparison to placebo groups where somnolence (9.8%), headache (9%), dizziness (7.8%) and nausea/vomiting (7.5%) were most frequent. These results are from data collection obtained from 1748 patients receiving gabapentin in different clinical trials. The overall proportion of patients reporting side effects during gabapentin therapy has been calculated to be 75% versus 55% of placebo [258]. These findings are confirmed by other clinical trials in which gabapentin have been tested for different types of neuropathic pain disorders. In these studies the most common side effects were somnolence, dizziness, ataxia and peripheral edema and the withdraw proportion due to side effects ranges from 8% to 19% of participants [263]. Other less common side effects, but also reported in different clinical trials are reported in Table 1.4 [257].

BODY AS A SYSTEM ADVERSE EVENTS	GABAPENTIN* N= 543 %	PLACEBO* N=378 %
Body as a whole:		
Fatigue	11	5
Weight increase	2.9	1.6
Back pain	1.8	0.5
Peripheral edema	1.7	0.5
Cardiovascular:		
Vasodilatation	1.1	0.3
Digestive system:		
Dyspepsia	2.2	0.5
Mouth or throat dry	1.7	0.5
Constipation	1.5	0.8
Dental abnormalities	1.5	0.3
Increased appetite	1.1	0.8
Hematologic and Lymphatic:		
Leukopenia	1.1	0.5
Musculoskeletal system:		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous system:		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.8
Thinking abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination abnormal	1.1	0.3
Respiratory system:		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and appendages:		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogential system:		
Impotence	1.5	1.1
Special senses:		
Diplopia	5.9	1.9
Amblyopia	4.2	1.1
Laboratory deviations:		
WBC decreased	1.1	0.5

*Plus background epileptic drug therapy.

Table 1.4 - Side effects: Incidence of side effects of gabapentin in comparison to placebo [218]

SUMMARY

CMM is a muscle pain disorder that is constantly present in the masticatory muscle for a minimum of six months. Its pathophysiology is not completely elucidated but it is thought to be influenced in great part by the CNS with continuous firing of pain signals to the brain, leading to constant pain in the masticatory muscles area. However, other psychological and peripheral influences to this condition have been also suggested.

There are no specific epidemiologic studies reporting the prevalence of this condition in the general population. However, it is a sub-diagnosis of TMD, which are present from 40 to 60% of the population and are significantly prevalent in women. The main clinical characteristics are associated with constant pain without periods of remission for more than six months, which eventually interferes with jaw function. Depression, anxiety and sleep disturbances are often associated in some cases. There is also a significant overlap of CMM with fibromyalgia, since these conditions may be present simultaneously in 75% of patients experiencing fibromyalgia.

There is no unique treatment for chronic pain. CMM should be addressed from different perspectives in order to achieve the best clinical results. Management strategies for CMM include peripheral, pharmacological and psychological therapies. The most common and effective local therapies are occlusal splint appliances and physical therapy. Pharmacological therapies include central-acting medications such as TCAs and opioids. NSAIDs and muscle relaxants can be palliative when administered for short periods of time. Finally psychological therapies, include biofeedback; stress and pain management skills; and counselling to address depression and

anxiety problems.

Gabapentin is a new generation antiepileptic agent that was initially developed to imitate GABA, but it has been showed to act blocking calcium channels instead of binding to GABA receptors. It also appears to indirectly increase GABA in the brain and block NMDA receptors. However, these are only proposed mechanisms of action and further research is required to fully elucidate its analgesic mechanism of action. The use of gabapentin in orofacial has been mainly associated to neuropathic pain problems and migraine prophylaxis. It has also been used anecdotically in the treatment of chronic musculoskeletal conditions. There are no trials with first-line EBM levels to show its efficacy in orofacial pain conditions. It has also been reported that gabapentin has a positive effect on sleep architecture as appears to increase sleep stages 3 and 4.

Gabapentin's half-life is 5 to 7 hours and it should be administrated 3 to 4 times per day to maintain adequate levels of the medication in the blood through the day. Dosage should be titrated slowly by 300 – 400 mg every three days until reaching a maintenance dose of 1200mg/day. Doses higher than 1200mg/day can also be provide increase efficacy but there is a greater chance of increasing the incidence of side effects. However, the use of doses of 3600mg/day has been reported in different clinical trials. The main side effects reported in the literature associated to gabapentin are dizziness, drowsiness and ataxia.

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chapter 2: RESEARCH PROJECT

Analgesic action of gabapentin on chronic pain in the masticatory muscles: a randomized controlled trial

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2.1 INTRODUCTION

TMD is a broad diagnostic term that includes a variety of sub-diagnostic categories that may require different treatments. Unfortunately most published studies do not make specific differentiation (e.g. mechanical articular problems, muscular problems, inflammatory joint problems) of these categories when evaluating a pharmacological therapy. Furthermore, most studies do not differentiate between acute, chronic or inflammatory pain.

Chronic masticatory myalgia (CMM) is part of TMD. It is characterized by constant pain of the masticatory muscles for greater than six months. During this time, sensitization of central components can occur[1 2-5], along with psychological [2 6-10] and peripheral factors [3 11-14] causing a persistent pain problem. CMM is not an easy entity to treat; therefore research to develop quality treatment tools is necessary.

Among the antiepileptic agents, gabapentin is used to treat different types of facial pain. Gabapentin is approved by the FDA for treatment of epilepsy and post-herpetic neuralgia. However, this medication has been used and tested for many other conditions in clinical practice and research studies [15 16]. Traditionally, the use of this medication in CMM has been based on past

clinical experience, training, practice traditions and the opinion of recognized authorities. To date, there are no clinical trials in the literature evaluating the analgesic efficacy of gabapentin specifically on chronic musculoskeletal pain. From an orofacial pain perspective, there is a lack of well-controlled clinical trials to give sufficient scientific support for the use of gabapentin in clinical practice for the treatment of CMM. Therefore, higher levels of EBM research (randomized controlled clinical trials) are required to determine the analgesic effect of gabapentin on chronic masticatory musculoskeletal pain.

For this reason, a randomized controlled clinical trial was conducted to assess the analgesic action of gabapentin on chronic pain in the masticatory muscles. The objectives of this study were:

Primary:

1) To compare the effectiveness of gabapentin versus placebo on reducing pain intensity reported by subjects with CMM, after 12 weeks.
2) To compare the effectiveness of gabapentin versus placebo on reducing palpable tenderness in masticatory muscles, in subjects with chronic masticatory myalgia after 12 weeks.

Secondary:

1) To compare the effectiveness of gabapentin versus placebo on reducing the impact of chronic pain on quality of life, reported by these subjects after 12 weeks.

2.2 METHODS AND MATERIALS

2.2.1 SUBJECTS

The protocol of this study was approved by the University of Alberta Human Ethics Research Board and by Health Canada (Appendix 1 and 2). Dentists within the city of Edmonton and surrounding areas were contacted by mail requesting referral of patients presenting with CMM (Appendix 3). Newspaper advertisements in Edmonton and poster advertisements at the University of Alberta campus were also utilized to recruit subjects (Appendix 4). In addition, existent patient charts of the TMD/Orofacial Pain Clinic were reviewed to identify potential candidates with CMM. Potential candidates were contacted via telephone for screening and recruitment. The sample size for this clinical trial was calculated based on the effect size approached in the study performed by Rowbotham et al. [17]:

Sg^2 = $(2.1)^2$ ------- change in pain score variance treated with gabapentin

Sp^2 = $(1.6)^2$ ------- change in pain score variance treated with placebo

Δ = -2.1 – (-0.5) ---- **Δ** = -1,6 ----- difference between pain scores reduction treated with gabapentin

For an 80% of power and significance level $\propto = 0.05$:

$$n = \frac{(Sg^2 + Sp^2) \times (1.96 + 0.85)^2}{\Delta^2}$$

$$n = \frac{(2.1^2 + 1.6^2) \times (1.96 + 0.85)^2}{(-1.6)^2}$$

$$n = \frac{6.97 \times (7.8961)}{2.56} \qquad n = 21.49 \text{------} \underline{\mathbf{n = 22}}$$

22 subjects were needed in each treatment group, for a total of 44 subjects. The sample size was set at 50 subjects in order to account for dropouts.

Inclusion criteria for subjects' participation in this study included:

- Females, 18-45 years of age.
- Diagnosis of CMM based on the classification I.a. of Dworkin and LeResche [18], "patients must present constant pain or ache in their masticatory muscles, face, and preauricular area or inside the ear at rest or during function."
- Subjects with pain of the masticatory muscle for at least 6 months.
- Chronic masticatory muscle pain not attributable to recent acute trauma or previous infection.
- Chronic pain in the masticatory muscles not attributable to an active inflammatory cause.
- Subjects able and willing to take oral medication.
- Moderate or severe baseline score of 50mm or greater using a 100mm VAS.
- Pain upon palpation at least in three of the following points proposed by Fricton et al. [19]: Temporalis: anterior, middle and posterior belly. Masseter: deep belly, and the inferior and anterior portion of the superficial belly. These points were selected for this study they allow for objective palpation procedure with an algometer.

Exclusion criteria included:

- Subjects with clinical evidence of an inflammatory TMD
- Pregnant or nursing females.
- Subjects presenting any of the following conditions: epilepsy, cardiac, renal and hepatic disorders.
- Subjects with intolerance to Gabapentin or to any of the components of the formulation.
- Subjects with dental or periodontal disease, oral pathological lesions, oral infection, or neuropathic facial pain.
- Subjects unwilling to discontinue therapy of previous analgesics or anti-inflammatory medications for a washout period.
- Subjects taking anticoagulant medications such as Warfarin.
- Subjects with occlusal splint appliance for less than six months.

2.2.2 RESEARCH TOOLS AND OUTCOME MEASURES

2.2.2.1 Visual Analogue Scale (VAS)

Subjects were asked to report their average pain intensity experienced in the last week on a VAS (VAS-pain). The validity and reliability of these methods for determining pain intensity, has been reported and confirmed in the literature [20-23].

The VAS has a rectangular shape of 10cm long with both ends labeled with the two extremes boundaries of pain sensation: "no pain", at one end and "worst pain imaginable" at the other end. This scale was contained on a plastic card, manufactured by Astra Pharma Inc. Scoring was accomplished by having subjects point out their pain intensity on the line. On the back of the card, there was a numerical scale to facilitate quick visualization of the number representing the subject's pain. It was a horizontal line, because it has been shown to produce a more uniform distribution of scores than a vertical VAS [23]. Based on the study performed by Collins et al [24], moderate pain was considered to be over 30mm, and severe pain over 54mm. A pain reduction of 30% on the 10cm VAS from the baseline pain scores, was considered to be clinically significant, based on the study of Farrar et al [25].

A secondary objective and outcome measure of the study was to obtain a general idea on how much CMM was affecting normal daily activities of the subjects in the study (VAS-function). For this purpose subjects were asked to report the subjective impact of their pain on daily functioning on

the 100mm VAS. They were trained to understand that zero represented no impact at all, and ten was representative of extreme or severe impact, reflecting disability.

2.2.2.2 **Pressure Algometer and Fricton's Craniomandibular Palpation Index**

A pressure algometer was utilized to perform extraoral palpation of the masticatory muscles. The pain threshold is a subjective point equivalent to the minimum pressure which induces a painful sensation. This instrument was selected due to the subjectivity that could result by the interpretation of pain response obtained with traditional manual palpation and that different examiners may palpate applying diverse amounts of pressure. This instrument allows the application of pressure over a specific area at constant, invariable rate, thereby approaching standardization [26]. Clinical reliability and validity of pressure algometry when used by different examiners have been reported [27-29 30]

The *Baseline push/pull dynamometer (GNR Orthopaedic and Rehabilitation Products, Ocala FL, USA)* was used in this clinical trial. This algometer presents a metal plunger with a rubber tip 1cm in diameter, mounted on a gauge calibrated in Kg/cm^2 or Newtons. This tip was placed in a direction perpendicular to the surface to be examined. Pressure exerted in the plunger was transmitted to the body and moved the indicator needle of the gauge in a clockwise direction. The maximum pressure remained on the gauge until the zeroing knob was pressed. This allowed the reading to be made after removal of the algometer from the body.

Extraoral palpation of the masticatory muscles was performed with the algometer using the following points described by Fricton et al [19 31 32]:

- Temporalis
  - Anterior portion
  - Middle portion
  - Inferior portion
- Masseter
  - Superficial belly, superior portion
  - Superficial belly, inferior portion
  - Deep belly

Procedure:

Based on the study performed by Fisher in 1987 [28], the palpation procedure consisted of three steps. First, the subject was instructed to say "yes" as soon as pain sensation began to be felt. Secondly, the rubber tip of the algometer was placed on the point to be examined, with the metal rod perpendicular to the surface to be palpated, and pressure was continuously increased by 1Kg/sec until the subject said "yes". Thirdly, at this moment, the tip of the algometer was removed from the subject, and the value of the pain threshold indicated was recorded. During this procedure, the examiner braced the subject's head with the open palm of the opposite hand in order to prevent any displacement while applying pressure

The subjects response was considered as "positive" when they experienced pain in a palpation site at a lower pain threshold value than the normal value for the muscle palpated. Those readings that

are equal or greater than the normal values were recorded as "negative" responses. The overall score for pain threshold of the masticatory muscles was quantified by adapting Fricton's Craniomandibular Palpation Index [19] to the number of palpation sites to be evaluated in this clinical trial. A value of *1* was assigned for each positive response and *0* for each negative response. The modified "palpation index" (PI) was calculated by using the sum of positive responses, divided by the total number of palpation points (12, in this case).

The normal values for masticatory muscles pain threshold used in this study were based on those reported by Chung et al. for female subjects [33]. These values were converted to Kg/cm², according to the formula Kg=0.0102 x KPa/KPa. The values are presented in Table 2.1.

Masticatory muscle palpation site	Normal value for pain threshold (kg/cm²)
Anterior temporalis	1.84
Middle temporalis	2.18
Posterior temporalis	2.26
Superficial, superior masseter	1.51
Superficial, inferior masseter	1.41
Deep masseter	1.54

Table 2.1 - Palpation threshold values. Normal threshold values for female subjects upon palpation with an algometer on the masticatory muscles [33].

Three final outcome measurements for each subject were recorded at the end of the study:

1- Initial and final pain intensity scores (average of one week) reported by the subject on the 10cm VAS (VAS-pain).

2- Initial and final pain values in the masticatory muscles upon palpation, calculated by the Palpation Index (PI).

3- Initial and final scores of the impact of the chronic pain in subject's quality of life, reported on the 10cmVAS (VAS-function).

Statistical analysis included a comparison of means utilizing a multivariate analysis of variance (MANOVA) for the outcome measures between the placebo and gabapentin group. The mean proportion (percentage) of the difference from the baseline scores (T1) to the final visit (T4) was compared in this MANOVA for the VAS-pain, PI and the VAS-function and is presented in the Results section. A Pearson correlation analysis to evaluate the association between reported pain on the VAS and the PI was conducted. This correlation analysis was performed utilizing the reduction percentage from T1 to T4. The mean reduction scores of the 3 outcome measures were compared throughout each one of the four study visits also utilizing a MANOVA.

2.2.5 **RANDOMIZATION, DOUBLE-BLINDING AND MEDICATION DOSING**

The 50 recruited subjects were randomly allocated into two study groups. One group consisted of 25 subjects to receive gabapentin, and, a second group consisted of 25 subjects receiving a placebo medication. A computer-generated randomization code list was utilized to randomly allocate subjects in these two groups in the same order as they were recruited into the study.

Pharmascience Inc. donated the medication for the study. A total number of 30,000 capsules of gabapentin 300mg and 700 capsules of gabapentin 100mg were received along with 40,790 capsules of 300mg placebo and 700 capsules of 100mg placebo. Correspondent pharmaceutical analysis tests for the placebo medication were performed by Pharmascience Inc. (PMS) prior to shipment to our clinic. The expiration date of gabapentin and placebo medication was August 2004. In order to blind this study, the placebo medication was packed in identical capsules to those of PMS-Gabapentin. They were administered to subjects in equal clear-plastic bottles identified with labels according to Investigational Pre-Packing Control Records, established by section C.05.011 of the Food and Drug Regulations. Non-used capsules of gabapentin and placebo were destroyed at the end of the trial by the Department of Pharmacy at the University of Alberta.

Gabapentin was administered until adequate pain control was reached or unacceptable side effects limited titration [34] [35]. In order to avoid side effects, provide adequate pain control and diminish as much as possible the number of drop-outs from the study, the minimum effective dose for each subject was determined. Subjects were started on 300mg per day and the dose was increased by 300mg every three days until pain was controlled with no adverse effects. The maximum dose was 4,200mg. Data from previous clinical trials suggest that doses higher than 1,200mg per day may have increased efficacy in some subjects, but at the same time there is the chance of minor side effects [36]. Therefore, subjects in this study received a weekly follow up phone call by a research assistant in order to help them reach their minimum effective dose and monitor for possible side effects. The dosing and titration protocol designed for this study is presented in Table 2.2

If the study medication had to be discontinued for any reason, dosage was gradually decreased by 300mg every three days. In the case of undesirable side effects, specific complaints were recorded, and the subject was expected to return to their clinical trial appointments for further evaluation, regardless if they had withdrawn from the study. This same discontinuation protocol was followed at the end of the study in those subjects who did not wish to continue taking gabapentin.

Days	Capsules per day	Mg per day	Daily dose (capsules) distribution
1-2-3	3 (100mg)	300mg	AM: one / Noon: one / PM: one
4-5-6	6 (100mg)	600mg	AM: two / Noon: two / PM: two
7-8-9	3 (300mg)	900mg	AM: one / Noon: one / PM: one
10-11-12	4 (300mg)	1,200mg	AM: one / Noon: one / PM: two
13-14-15	5 (300mg)	1,500mg	AM: one / Noon: two / PM: two
16-17-18	6 (300mg)	1,800mg	AM: two / Noon: two / PM: two
19-20-21	7 (300mg)	2,100mg	AM: two / Noon: two / PM: three
22-23-24	8 (300mg)	2,400mg	AM: two / Noon: three / PM: three
25-26-27	9 (300mg)	2,700mg	AM: three / Noon: three / PM: three
28-29-30	10 (300mg)	3,000mg	AM: three / Noon: three / PM: four
31-32-33	11 (300mg)	3,300mg	AM: three / Noon: four / PM: four
34-35-36	12 (300mg)	3,600mg	AM: four / Noon: four / PM: four
37-38-39	13 (300mg)	3,900mg	AM: four / Noon: four / PM: five
40-41-42 to 90	14 (300mg)	4,200mg	AM: three / Noon: five / PM: five

Table 2.2 - Dosage titration protocol: Dosage titration dosage for the study drug utilized from day 1 to 40. After day 40, the dose was maintained at a maximum of 4200mg. If this maximum dose was not reached due to pain control with a lower dose or side effects, subjects were maintained at their minimum effective dose.

Acetaminophen 500mg was utilized in this study for break-through pain in those cases where subjects needed pain control between gabapentin doses, or if the study medication was not having an analgesic effect. Subjects in both study groups were provided with bottles of acetaminophen

500mg with 500 capsules. They were instructed to take it as needed every six hours, with a maximum of eight tablets (4,000mg) per day.

2.2.6 CLINICAL PHASE AND DATA COLLECTION

This clinical trial was designed to run for a total of 12 weeks. Subjects were expected to return for follow up consults every 4 weeks.

First Visit (T 0): At this time pretreatment information about the subjects was collected, including personal information, age, medical history information, current medications, and data regarding chief complaint (onset, initiating factors, localization, severity, duration of symptoms, aggravating and alleviating factors). An intraoral examination was performed in order to identify any possible pathology related to soft or hard tissues. This information was recorded in a data collection sheet for the initial evaluation (Appendix 5). Palpation of the temporomandibular joints was done in order to rule out TMJ inflammatory pathology such as capsulitis and degenerative joint disease.

Subjects were also asked to indicate their pain intensity average for the last week using the VAS. It is reported in the literature, that the analgesic activity has an adequate sensitivity in clinical trials when pretreatment pain is of a moderate to severe intensity [26]. Therefore, for this study, subjects with a score of 5 or greater in the VAS were included.

If the subject was considered to be eligible for the study, informed consent documentation was discussed. The study protocol was reviewed with each patient and the primary investigator was available to answer questions. Written material explaining the study was also provided (Appendix 6). Subjects who agreed to participate in the study completed the written consent form (Appendix 7). Patient's authorization to contact his/her family physician was also requested.

The family physician was contacted in order to inform him/her that the patient might receive gabapentin in this study and to assure that there was no medical contraindication (Appendix 8). For blinding purposes, the family physician was not informed regarding the group to which the subject was randomly allocated.

Subjects were asked to discontinue any pain medications taken on as needed basis such as anti-inflammatories, muscle relaxants or combination drugs (i.e. acetaminophen and narcotics). The only drug allowed for breakthrough pain during the study was acetaminophen, and therefore, subjects were not asked to discontinue this medication if they were taking it. In those cases in which a pain medication was required to be discontinued, subjects returned for a second visit after the washout period. The washout period for discontinuation of therapy with these medications was based on the half-life of the drug. If subjects were taking medications on a regular basis for more than two months such as TCAs, benzodiazepines, specific serotonin re-uptake inhibitors (SSRIs), among others, they were allowed to participate in the study as long as no changes in the dosage of these medications were performed during the course of the study. In addition, other medications that could influence pain, such as sedative hypnotics, were not allowed to be taken as needed (not on regular basis) during the course of the study to avoid changes and bias in pain perception.

If eligible subjects were not taking any pain medication at the time of the study, they were asked to return for a second visit, as soon as their family physician consented to the subject's participation.

Second Visit (T 1):

In this visit, subjects were asked to indicate on the VAS their average pain intensity during the last week. Once these values were recorded, they were also asked to report the impact of their masticatory muscle pain on their daily functioning and normal activities on the VAS. These values were recorded as baseline scores for pain intensity levels and impact on daily functioning.

After this information was recorded, extraoral palpation of the muscles of mastication was performed with the algometer. The pain threshold values were recorded in Kg/cm^2, and also as positive and negative responses, as previously described.

The data obtained from this visit, was collected in a patient data collection sheet (Appendix 9). Once the pretreatment data was collected, subjects were randomly allocated into one of the two study groups and were also provided with the study medication (gabapentin or placebo) by a research assistant. Finally, the subjects were asked to report in a 4-week record form (Appendix 10) any side effects and also, when and how much acetaminophen was taken. In addition, subjects received a weekly telephone follow-up by a pharmacy research assistant in order determine the minimum effective dose for each subject and possible side effects. This data was recorded in a telephone follow-up record sheet (Appendix 11)

***(T-2)* Third Visit (week 4) – *(T-3)* Fourth Visit (week 8)**

With both of these visits, the subject self-report of masticatory muscle pain intensity was recorded on the VAS. Extraoral palpation of masticatory muscles and record of pain intensity were performed following the same protocol used for the first visit.

The subject's 4-week record form was assessed to monitor side effects and amount of acetaminophen intake. The next batch of study medication and acetaminophen was dispensed. A new record form was dispensed to record side effects and acetaminophen intake during the next 4 weeks. In addition, between each visit, subjects continued receiving weekly telephone follow-up consults by a research assistant

(T-4) Fifth Visit (week 12)

Finally, subjects were asked to return for their last visit at week twelve (90 days). Data collection protocol for this appointment was similar to the last three visits previously described. Final data was collected at this time. This data was utilized in statistical analyses as final pain scores. At this point, the medication code was not broken but subjects were able to receive active treatment for pain relief.

A post-treatment consultation was scheduled with an un-blinded physician in order to provide the patient with information and medical advice on how to proceed with additional medical pain management. During this consult, the randomization code was broken to the subject but not to the

main investigator. In those cases in which gabapentin was effective and the subject wanted to continue receiving treatment, gabapentin prescriptions for therapy continuation were provided. In those cases where gabapentin was ineffective or if the patient received placebo and required additional pain management, other treatment options were offered as needed in each case. Subjects were given the option of continue care in the TMD/ Orofacial Pain Clinic, Department of Dentistry at the University of Alberta. Finally, the patient's family physician was contacted by written correspondence in order to provide update on the patient's progress and further recommendations for chronic orofacial pain management (Appendix 12).

2.2.8 **INTENT-TO-TREAT ANALYSIS**

The results of this clinical trial statistically analyzed with a MANOVA to determine if there was a statistically significant mean pain reduction between the gabapentin and placebo groups in the three outcome measures (VAS-pain, PI and VAS-function). Statistical analysis was performed with the population that completed the trial and also with an "intent-to –treat" population, through "intent to treat" analysis.

Intent to treat analysis, more than being a statistical test, represents a methodology design for clinical trials. It is associated to the subject population to be included in the statistical tests [37]. The intent to treat analysis includes all randomized subjects in the groups to which they were randomly assigned, regardless of their adherence to the entry criteria, the treatment they actually received, subsequent withdrawal from treatment or deviation from the protocol [38 39].

Followers of the "intent-to-treat philosophy", support their theory in three main principles. The first one is that intent to treat analysis holds the randomization as of paramount importance. If subjects were randomized at the beginning of the protocol, this should be respected and it is not recommended to discriminate which subjects should be included for statistical analysis. Deviation from the original randomized groups can contaminate the treatment comparison [39]. The second premise has to do with compliance of treatment. Data derived from those subjects who were not compliant with the treatment should be also included for statistical analysis. The statistical reason being is that compliance or non-compliance occurs after randomization, and attempting to account for noncompliance by excluding noncompliant subjects can bias treatment evaluation. In addition, in real clinical practice, there is always a proportion of subjects that are not fully compliant, and, compliant subjects usually have better outcomes than noncompliant subjects, regardless of treatment [38 39]. The third premise of intent-to-treat is associated to withdrawal from the clinical trial. Data derived from subjects who withdraw from the study and no longer receive treatment should be included in the statistical analysis. After all, subject withdrawal occurs after randomization and might be treatment related. Excluding subjects who withdraw could bias results [38].

Hypotheses from clinical trials can be either "pragmatic" or "explanatory". Pragmatic hypotheses aim to identify the utility of a treatment for clinical practice. Explanatory hypotheses tend to isolate and identify the pure biologic effect of the treatment [40]. Although both hypotheses are important they cannot always be addressed together in the same clinical trial. The intent-to treat philosophy is focused on the pragmatic hypotheses and effectiveness analysis of a treatment on a whole population, being very significant for clinical practice [37]. On the other hand, by excluding those subjects who did not completed the trial for any reason, an explanatory hypotheses is followed,

trying to determine the pure biological efficacy of a certain treatment [40]. The investigator is free to choose on which of these two theories the clinical trial design will be based [39]. The main disadvantage of a subset efficacy analysis is that a bias in subject subset selection will bias the treatment group comparison [39]. The principal concern with intent-to-treat analysis, on the other hand, is that the power of the study to detect the specific beneficial treatment effect will be lower than the one present in an efficacy test [39].

Non compliance to research treatment, withdrawals and deviation to the protocol during the trial can lead to missing data. Missing data do not bias the comparison of treatment groups [39], however it is important to deal with it for statistical purposes. To avoid missing data as much as possible, the intent-to-treat design requires that all subjects continue to be followed, including those who for any reason no longer receive treatment. This tends to be especially powerful when an effective treatment decreases the progression of a disease during its administration. Thus, a subject may still benefit after the treatment is no longer received [39]. In this sense, the investigator is able to proceed with both, an intent-to-treat analysis and also an efficacy analysis, if desired [39]. For this reason, in this clinical trial, subjects who were no longer receiving study medication (gabapentin or placebo) were expected to be evaluated as initially scheduled in order to have follow-up data to be included in the final analysis.

Statistical methods to deal with incomplete observations were applied for those cases in which subjects wouldn't show up for their appointments and there would be missing data. The majority of these methods require the assumption that censored or missing data occur completely at random [39]. The method used in this study to deal with incomplete observations was the Last Observation

Carried Forward (LOCF). In this method, the last observation obtained from a subject is substituted for all subsequent missing follow-up observations [39]. In this study, subjects who, once randomized, had evidence of taking at least on dose of the study medication and provided at least 1 follow-up evaluation were include for intent-to-treat analysis. This way of dealing with incomplete observations has also been done in other RCTs, such as the one conducted by Rowbotham et al in 1998 [17].

2.3 **RESULTS**

A total of seventy nine subjects were interviewed and clinically screened in a period of seven months to obtain the required 50 subject sample enrolment. Thirty six (72%) subjects completed the study at week 12. From the 36 subjects who completed the trial, 19 (38%) were in the gabapentin group and 17 (34%) in the placebo group. From the 14 (28%) subjects who dropped out the clinical trial, 7 (14%) subjects were noncompliant with the dosing and the scheduled appointments; 4 (8%) subjects stopped taking the study drug (gabapentin or placebo) due to side effects; and 1 (2%) subject had mild adverse reactions but was unsure if these were related to the study drug. One (2%) subject suspected of being pregnant right after beginning the trial, so she was advised to discontinue the medication immediately. Finally 1 (2%) subject was dropped out the study for starting a new pain medication that was not taken on a regular basis. The intent-to-treat population involved 44 subjects (88%), from which 24 (48%) were in the gabapentin group and 20 (40%) in the placebo group. Table 2.3 illustrates these results.

Female subjects	**Gabapentin**	**Placebo**	**Total**
Enrolled in the trial	25 (50%)	25 (50%)	50 (100%)
Completed the trial	19 (38%)	17 (34%)	36 (72%)
Drop outs	6 (12%)	8 (16%)	14 (28%)
Intent-to-treat population	24 (48%)	20(40%)	44 (88%)
Age range	19-45	19-45	19-45

Table 2.3 – Demographics table: This table shows the number and percentages of subjects in each study group who were enrolled in the trial, completed the trial and dropped out. The intent-to –treat population and patients' age-range is also included.

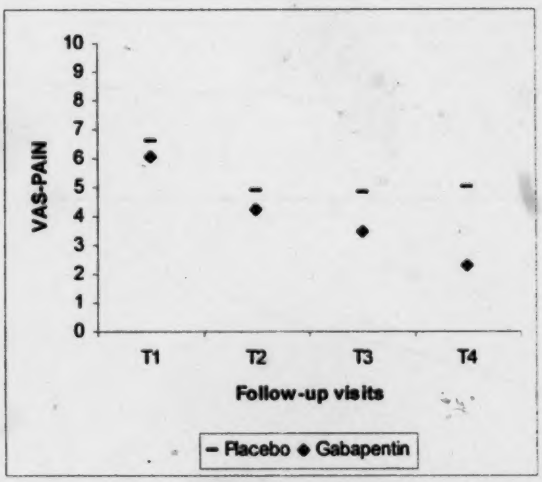
2.3.1 EFFICACY ANALYSIS

For the efficacy analysis only subjects who completed the trial at week 12 were considered. By a MANOVA means of the proportions of pain reduction were compared between the gabapentin and placebo group for the three outcome measures: weekly average of pain intensity on the VAS (VAS-pain), number of tender sites with the PI, and weekly impact of CMM on daily functioning reported on the VAS (VAS-function). For the VAS-pain, there was significant statistical pain reduction of 54.07% of the treatment group in comparison to the placebo, which had a 19.92% of pain reduction (P=0.021). This difference was also clinical significant, since 30% of pain reduction on the 10cm VAS is the minimum required for clinical significance [25].

For the PI a greater statistical difference was detected. The number of tender sites in the masticatory muscles upon palpation were reduced 79.84% in the gabapentin group compared to 11.76% in the group receiving placebo (P< 0.001). The reduction of CMM interference with daily functioning reported by subjects on the 10cm VAS was measured to be 57.70% in subjects taking gabapentin compared to 13.60% in those subjects receiving placebo (P=0.007).

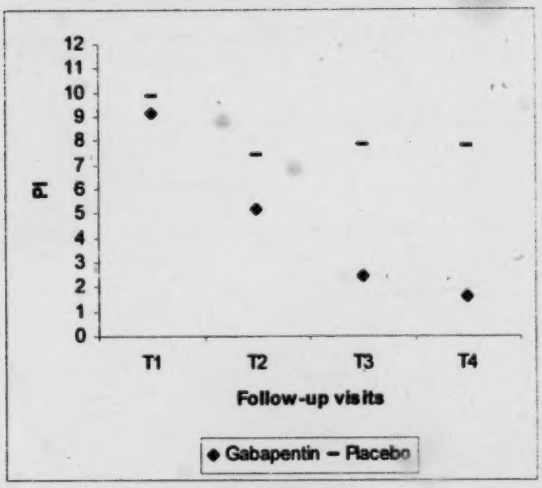
A correlation analysis was performed to determine the association between the reported pain in the VAS and the PI. A positive correlation was detected between the two variables, with Pearson correlation value of 0.775 for the gabapentin group and 0.627 for the control group. It was observed that the average pain reduction on the VAS (VAS –pain) increased along with the reduction of tender sites proportion in the PI. Figure 2.1 shows the correlation between these two variables.

Finally a general linear model was obtained to compare gabapentin and placebo efficacy in the three evaluated variables along the four visits of the clinical trial during the 12-week period. The average study medication dose is included for both groups. Figure 2.1, 2.2 and 2.3 illustrate the difference between responses to gabapentin and placebo for VAS-pain, PI and VAS-function, respectively.



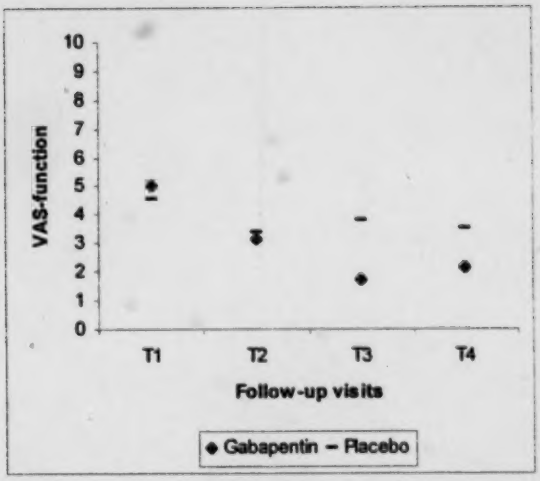
Visit	Gabapentin n=19	Gabapentin dose average (mg/day)	Placebo n=17	Mean difference	P value
T1	Mean=6.06 SD=1.32	300	Mean=6.56 SD=1.26	0.5	0.264
T2	Mean=4.22 SD=2.38	2463.15	Mean=4.91 SD=2.03	0.69	0.349
T3	Mean=3.46 SD= 2.27	3426.31	Mean=4.84 SD=2.49	1.38	0.098
T4	Mean=2.70 SD=2.17	3315.78	Mean=5.00 SD=2.88	2.3	0.011

Figure 2.1 – MANOVA: 12-week for VAS-pain (efficacy analysis): Gabapentin group (GBP) presents a mean VAS-pain baseline score of 6.06 at T1 and final scores of 2.70 at T4. Placebo group (PBO) presents a mean VAS-pain baseline score of 6.56 at T1 and final scores of 5.00 at T4.



Visit	Gabapentin n= 19	Gabapentin dose average (mg/day)	Placebo n= 17	Mean difference	P value
T1	Mean=9.15 SD=2.19	300	Mean=9.87 SD=2.02	0.72	0.326
T2	Mean=5.15 SD=3.67	2463.15	Mean=7.43 SD=3.44	2.28	0.069
T3	Mean=2.42 SD=2.52	3426.31	Mean=7.81 SD=3.83	5.39	<0.001
T4	Mean=1.63 SD=2.52	3315.78	Mean=7.75 SD=4.31	6.12	<0.001

Figure 2.2 – MANOVA: 12-week progress for PI (efficacy analysis): Gabapentin (GBP) and placebo (PBO) groups present a mean PI baseline score of 9.15 and 9.87, respectively on 12 palpation sites at T1. However, GBP showed a mean post-treatment score of 1.63, in comparison to 7.75 in PBO at T4.



Visit	Gabapentin n= 19	Gabapentin dose average (mg/day)	Placebo n= 17	Mean difference	P value
T1	Mean=5.04 SD=2.75	300	Mean=4.54 SD=2.27	0.5	0.550
T2	Mean=3.14 SD=2.57	2463.15	Mean=3.40 SD=2.64	0.26	0.773
T3	Mean=1.74 SD=2.10	3426.31	Mean=3.79 SD=2.64	2.05	0.016
T4	Mean=2.12 SD=2.44	3315.78	Mean=3.48 SD=2.95	1.36	0.143

Figure 2.3 – MANOVA: 12-week progress for VAS-function (efficacy analysis): Gabapentin group (GBP) presents a mean VAS-function baseline score of 5.04 at T1 and a final score of 2.12 at T4. The placebo group (PBO) presents a mean VAS-pain baseline score of 4.54 at T1 and final scores of 3.48 at T4.

The average doses for both study groups in the three follow-up visits are presented in table 2.4. It can be observed in figures 2.2, 2.3 and 2.4 how subjects in the gabapentin group begin to have a statistically significant improvement effect at T3 and T4.The average dose for the gabapentin group at these visits were 3426.31mg/day and 3315.78mg/day respectively. In these graphics the

analgesic effect of gabapentin appears to increase with the dose titration, in comparison to the placebo group, which maintains similar score levels throughout T2, T3 and T4.

2.3.2 INTENT-TO-TREAT ANALYSIS

The intent to treat population consisted of a total of 44 (88%) subjects. Twenty four (48%) subjects were in the gabapentin group and 20 (40%) received placebo. A subject was considered to be part of the intent to treat population when once randomized, had evidence of taking at least one dose of the study medication and provided at least 1 follow-up evaluation. Six (12%) subjects presented only for the initial visit when medication dosing was started. They did not present for follow up and no observation could be measured. Therefore, analysis for these subjects was not possible.

A number subjects in this study were on TCAs or SSRIs for more than two months, prior to enrolling into the trial (Table 2.4). No changes in the dosage of these medications were allowed during the trial. The number of subjects in the intent-to-treat population who were taking these agents is presented in table 2.4.

Other medication	Gabapentin n=24	Placebo n=20
TCA	none	2 (10%)
SSRI	8 (33%)	5 (25%)

Table 2.4 – Subjects taking other medications: Number of subjects in the intent-to-treat population taking TCAs and SSRI on a regular basis (unchanged dosage) during the study.

Subjects in the gabapentin group demonstrated a clinically and statistically significant reduction reported on the VAS-pain of 51.04% in comparison to 24.30% in the placebo group (P=0.037). The

proportion of tender palpation sites in the masticatory muscles based on the PI was reduced by 67.03% in the gabapentin group compared to 14.37% in the placebo group (P=0.001). Finally, the reduction of the impact of CMM on daily functioning reported on the VAS-function measure was 57.39% in subjects taking gabapentin, compared to 16.92% in the placebo group (P=0.022). Table 2.5 summarizes these results and makes a comparison between the efficacy analysis (EA) and the intent-to-treat analysis (ITT). Tables 2.6, 2.7 and 2.8 present percentages of subjects in both study groups with their improvement, at different levels of clinical significance, scored on the VAS-pain, PI and VAS-life, respectively.

Analysis	EA	EA	EA	ITT	ITT	ITT
Outcome measure	VAS-pain reduction (T1-T4)	PI reduction (T1-T4)	VAS-function reduction (T1-T4)	VAS-pain reduction (T1-T4)	PI reduction (T1-T4)	VAS-function reduction (T1-T4)
Gabapentin	54.07%	79.84%	57.70%	51.04%	67.03%	57.70%
Placebo	19.92%	11.76%	13.60%	24.30%	14.37%	16.92%
P value	0.021	0.000	0.007	0.037	0.001	0.022
n= 36/ gabapentin=19, placebo=17			n=44 / gabapentin=24, placebo=20			

Table 2.5 – MANOVA results for efficacy and intent-to-treat analyses: Comparison between the efficacy and intent-to-treat analysis on the three outcome measures: VAS-pain, PI and VAS-function.

Percentage of reduction scored in the VAS-pain	Gabapentin (n=24)	Placebo (n=20)
Negative responses	3 = 12.5%	6 = 30%
0 ----------19%	2 = 8.33%	2 = 10%
20 ----------39%	1 = 4.16%	3 = 15%
40 ----------59%	8 = 33.33%	4 = 20%
60 ----------79%	4 = 16.16%	2 = 10%
80 ----------100%	6 = 25%	3 = 15%

Table 2.6 – Clinical improvement in the VAS-pain: Indication of percentage of subjects with their correspondent pain reduction percentage scored in the VAS at different levels of clinical significance

Percentage of reduction scored in the PI	Gabapentin (n=24)	Placebo (n=20)
Negative responses	2 = 8.33%	5 = 25%
0 ----------19%	2 = 8.33%	7 = 40%
20 ----------39%	---	---
40 ----------59%	3 = 12.5%	2 = 10%
60 ----------79%	2 = 8.33%	2 = 10%
80 ----------100%	15 = 62.5%	3 = 15%

Table 2.7 – Clinical improvement in the PI: Indication of percentage of subjects with their correspondent reduction of pain upon palpation percentage scored in the PI, at different levels of clinical significance

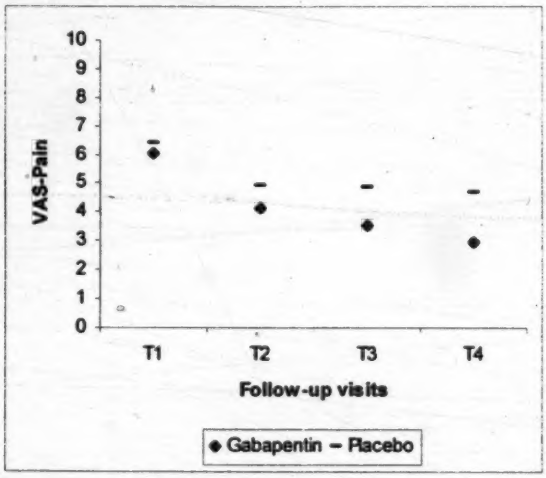
Percentage of reduction scored in the VAS-function	Gabapentin (n=24)	Placebo (n=20)
Negative responses	1 = 4.16%	6 = 30%
0 ----------19%	7 = 29.61%	6 = 30%
20 ----------39%	2 = 8.33%	1 = 5%
40 ----------59%	1 = 4.16%	1 = 5%
60 ----------79%	4 = 16.16%	3 = 15%
80 ----------100%	9 = 37.5%	3 = 15%

Table 2.8 – Clinical improvement in the VAS-function: Indication of percentage of subjects with their correspondent percentage of reduction of pain interference with daily functioning, scored in the PI, at different levels of clinical significance

A correlation analysis was performed to determine if a direct association was also present between VAS-pain and the PI variables in the intent-to-treat population. A positive correlation between the two variables was detected with a Pearson correlation value of 0.70 in the gabapentin group and 0.62 in the placebo group. This indicates that pain reduction increases simultaneously in the VAS-pain and also in the PI.

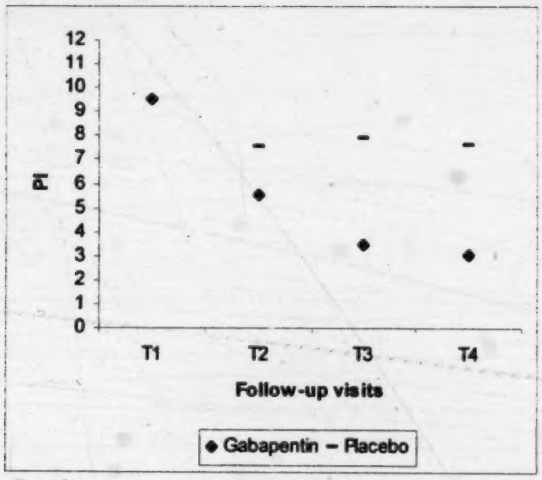
Finally, a MANOVA was performed to compare the means of the response to gabapentin of both study groups during the 12-week period for each variable evaluated (VAS-pain, PI and VAS-function). As in the efficacy analysis, the intent-to-treat population taking gabapentin showed a

significant pain reduction in the VAS-pain and PI, upon the second follow up visit (T2), when compared to the placebo group which maintained the same pain levels until the final visit (T4). Figures 2.4, 2.5 and 2.6 illustrate these differences.



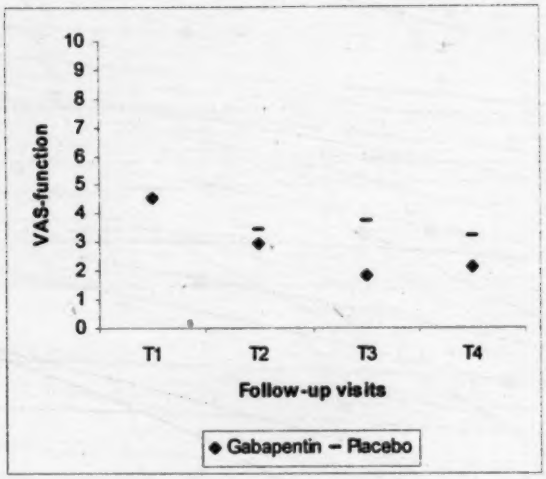
Visit	Gabapentin n=24	Placebo n=20	Mean difference	P value
T1	Mean=6.03 SD=1.27	Mean=6.41 SD=1.21	0.38	0.309
T2	Mean=4.13 SD=2.17	Mean=4.94 SD=2.00	0.81	0.209
T3	Mean=3.53 SD=2.12	Mean=4.86 SD=2.37	1.33	0.058
T4	Mean=2.94 SD=2.37	Mean=4.69 SD=2.67	1.75	0.026

Figure 2.4 – MANOVA: 12-week progress for VAS-pain (intent-to-treat analysis): Gabapentin group (GBP) presents a mean VAS-pain baseline score of 6.03 at T1 and final scores of 2.94 at T4. Placebo group (PBO) presents a mean VAS-pain baseline score of 6.41 at T1 and final scores of 4.69 at T4.



Visit	Gabapentin n=24	Placebo n=20	Mean difference	P value
T1	Mean=9.50 SD=2.187	Mean=9.50 SD=2.06	0	1.00
T2	Mean=5.54 SD=3.43	Mean=7.55 SD=3.51	2.01	0.063
T3	Mean=3.46 SD=3.28	Mean=7.85 SD=3.81	4.39	<0.001
T4	Mean=3.04 SD=3.85	Mean=7.60 SD=4.29	4.56	<0.001

Figure 2.5 – MANOVA: 12-week progress for PI (intent-to-treat analysis): Gabapentin (GBP) and placebo (PBO) groups present a mean PI baseline score of 9.50 on 12 palpation sites at T1. However, GBP showed a mean post-treatment score of 3.04, in comparison to 7.60 in PBO at T4.



Visit	Gabapentin n=22	Placebo n=18	Mean difference	P value
T1	Mean=4.58 SD=2.87	Mean=4.57 SD=2.18	0.01	0.985
T2	Mean=2.93 SD=2.58	Mean=3.41 SD=2.47	0.48	0.54
T3	Mean=1.82 SD=2.22	Mean=3.70 SD=2.48	1.88	0.013
T4	Mean=2.13 SD=2.50	Mean=3.22 SD=2.84	1.09	0.190

Figure 2.6 – MANOVA: 12-week progress for VAS-function (intent-to-treat analysis): Gabapentin group (GBP) presents a mean VAS-pain baseline score of 4.583 at T1 and final scores of 2.138 at T4. Placebo group (PBO) presents a mean VAS-pain baseline score of 4.568 at T1 and final scores of 3.226 at T4. The difference between groups begins to appear at T2.

2.3.3 INCIDENCE OF SIDE EFFECTS

Side effects are reported based on the 50 subjects who enrolled in the study, including those who dropped out the study. For the gabapentin group, the incidence of reported side effects includes dizziness (28%), drowsiness (24%), memory and cognitive impairment (16%); fatigue (8%), and

dry mouth (8%). Other reported side effects, with an incidence of 4%, in this group include ataxia, diarrhea, chest tightness, constipation and weight gain.

On the other hand, the placebo group demonstrated the following incidence of side effects: drowsiness (20%), fatigue (8%) and dizziness (8%). An incidence of 4% was detected for numbness, memory and cognitive impairment, diarrhea, accelerated heart beat and dry mouth. Table 2.9 compares the side effects reported in the gabapentin and placebo groups.

Side effect reported	Gabapentin (n=25)	Placebo (n=25)
Dizziness	28% (n=7)	8% (n=2)
Drowsiness	28% (n=7)	20% (n=5)
Memory and cognitive impairment	16% (n=4)	4% (n=1)
Dry Mouth	12% (n=3)	4% (n=1)
Fatigue	12% (n=3)	8% (n=2)
Ataxia	4% (n=1)	Not reported
Diarrhea	4% (n=1)	4% (n=1)
Constipation	4% (n=1)	Not reported
Weight Gain	4% (n=1)	Not reported
Chest tightness	4% (n=1)	Not reported
Numbness	Not reported	4% (n=1)
Accelerated heart beat	Not reported	4% (n=1)

Table 2.9 - Side effects: Comparison of the incidence of adverse reactions between gabapentin and placebo groups. Dizziness and memory/cognitive impairment were the most pronounced side effects of gabapentin in comparison to placebo in this clinical trial.

The most common side effects caused by gabapentin, such as dizziness, and cognitive impairment mainly occurred at early doses (300mg-1200mg), when subjects were starting treatment. They were also observed, although less frequently, right after increasing the dose during the titration phase. These side effects were not serious enough for subjects to withdraw from the study, since they were easily managed with specific-patient dosing and weekly orientation by the research assistant.

Of the 14 (28%) drop outs in this study, only 4 (8%) withdrew due to side effects. Two (4%) of them were in the gabapentin group and the other two (4%) received placebo. The 2 subjects who dropped out the gabapentin group experienced drowsiness and cognitive impairment. The 2 subjects who withdrew from the placebo group experienced drowsiness.

In this study, side effects were not severe enough to prevent any subject from achieving minimum effective dose (therapeutic dose). Subjects who, had only partial pain control or no pain control, were taking the maximum dose established in our study protocol (4200mg/day) and it could not be determined if further dosage titration would have had an analgesic effect for these subjects. According to side effects, dose titration and pain control, the percentage of subjects in both study group in the following cases were analyzed (Table 2.10 illustrates these cases):

1. Subjects who achieved minimum effective dose (MED) without side effects (w/o SE), and obtained complete pain control (CPC).
2. Subjects who achieved minimum effective dose (MED) with manageable side effects (SE) during titration, and obtained complete pain control (CPC).
3. Subjects who achieved maximum dose (MAXD) without side effects (w/o SE) during titration, and obtained partial pain control (PPC).
4. Subjects who achieved maximum dose (MAXD) with manageable side effects (SE) during titration, and obtained partial pain control (PPC).
5. Subjects who achieved maximum dose (MAXD) without side effects (w/o SE) during titration, and did not obtain pain control (NPC).

6. Subjects who achieved maximum dose (MAXD) with manageable side effects (SE) during titration, and did not obtain pain control (NPC).

Based on subjects who completed the trial (efficacy analysis population), 4 (21.05%) subjects within the gabapentin group were able to obtain complete pain control at their minimum effective dose, with no side effects. The same situation occurred in only 1 (5.88%) subject of the placebo group.

In the gabapentin group 8 (42.10%) subjects were able to achieve complete pain control at their specific therapeutic dose, but experienced side effects during dose titration. However, these side effects were mild and disappeared within a few days and did not prevent subjects from achieving a therapeutic dose with pain control. This situation was only seen in 1 (5.88%) subject in the placebo group.

All subjects who only obtained partial pain control were titrated up to the maximum dose proposed in this study (4200mg/day) and further dose increment could not be continued. One (5.26%) subject in the gabapentin group reached maximum dose with partial pain control and no side effects. Four (21.05%) subjects if the same group experienced side effects during dose titration until reaching maximum dose with only partial pain control.

Only 2 subjects within the gabapentin group did not achieve pain control and reached maximum dose. One (5.26%) of these subjects was able to achieve the maximum dose without experiencing any side effects. The other subject (5.26%) experienced mild side effects that disappeared and did

not prevent her from taking the maximum dose. However, in the placebo group 7 (41.17%) patients did not experience pain control and reached maximum dose with no side effects. On the other hand, control subjects 8 (47.05%) experienced manageable side effects during titration up to maximum dose with no pain control.

Side effects, dose titration and pain control	Gabapentin (n=19)	Placebo (n=17)
MED – w/o SE - CPC	4 = 21.05%	1 = 5.88%
MED – SE - CPC	8 = 42.10%	1 = 5.88%
MAXD – w/o SE - PPC	1 = 5.26%	Not observed
MAXD – SE - PPC	4 = 21.05%	Not observed
MAXD – w/o SE - NPC	1 = 5.26%	7 = 41.17%
MAXD – SE - NPC	1 = 5.26%	8 = 48.05%

Table 2.10: Therapeutic dose, side effects and pain control: Percentage of subjects in the gabapentin and placebo groups who were able to achieve their minimum effective dose (MED) dose with or without side effects (SE, w/o SE) and obtained complete pain control (CPC). It is also reported the percentage of subjects who achieved partial pain control (PPC) or no pain control (NPC) at the maximum dose (MAXD) with or without side effects (SE, w/o SE) in both study groups.

2.4 DISCUSSION

Physiological pain is usually short-lasting and has a protective role by warning that an injury has occurred and reduces risk of further injury. Usually, this pain is quickly resolvable and easy to treat. However, sometimes pain may also become persistent (chronic) with no biological role. Indeed, rather than simply being a symptom of a disease or injury, it could be considered a disease itself involving CNS perception disorders, psychological implications and sleep disturbances. CMM, as a chronic pain condition, is not easily treated and different therapies are generally required to obtain the best treatment outcomes. Pharmacotherapy is often utilized to treat and manage chronic pain. This study demonstrated that gabapentin is a treatment option to provide analgesia and anti-hyperalgesia in the pharmacological management of CMM.

The results of this clinical trial reject the proposed null hypotheses: gabapentin was statistically and clinically superior to placebo in reducing pain intensity on the VAS, number of tender sites on the PI and interference of CMM with daily functioning from baseline pain scores recorded at T1 until the end of the study at T4 (Table 2.5).

In this clinical trial gabapentin appears to have a statistically significant difference with the control group at T4 for the VAS-pain. For the PI the difference appears at T3 and it is maintained up to T4. At these points gabapentin dose was approximately 3300mg/day to 3600mg/day. This could be considered a threshold dose for analgesic efficacy in CMM. Maximum dose at T4 according to our titration protocol was 4200mg/day. However, the mean dose in the actual study was 3426.31mg/day at T3 and 3315.78mg/day at T4 because the minimum effective dose of some subjects was reached before reaching the maximum dose (4200mg/day). The mean dose may be

slightly lower at T4 since a small number of subjects decided to decrease their dose 300mg/day after T3. This is because they may have reached the minimum effective dose at some point before T3 and then realized that the analgesic effect was not different with further titration. The fact that a statistical difference appeared at T4 and not at T3 for the VAS-Pain may be related to the time that this drug takes to produce analgesic effect in CMM that is perceived by the subjects. It is important to remember that there is no consensus in the literature regarding the time required by the drug to produce its effect and it can range from weeks to several months when treating intractable pain conditions and varies from patient to patient [41]. In addition, gabapentin plasma level is dose dependent at doses up to 1200mg/day and this dose-dependency tends to decrease when titrating after 1800mg/day [36]. For this reason the analgesic effect appears and it is maintained at T4 for VAS-Pain and PI, respectively, although the dose is slightly lower at this visit.

In terms of side effects and dose titration, gabapentin did not cause side effects that were severe enough to prevent dose titration. In those cases in which side effects appeared during dose titration, they subsided within a few days and where easily managed. This allowed following the continuation of the dose titration protocol until a therapeutic dose was achieved. In this clinical trial, subjects who achieved partial pain control or no pain control at all were at the maximum dose proposed for this study (4200mg/day) and further dose titration could not be continued to determine if an increased analgesic effect is observable. Further research on gabapentin therapy for CMM or other chronic musculoskeletal disorders like fibromyalgia should address this question using doses higher than 4200mg/day.

From a clinical perspective, the results of this study demonstrate how 74% of subjects in the gabapentin group achieved a clinically significant difference in the VAS-Pain as they indicated pain reduction in this scale ranging from 40 to 100%. It can be observed how 80% of the subjects experienced from 40 to 100% reduction of hyperalgesia upon palpation, according to the PI. Finally, 57% of subjects reported that gabapentin therapy reduced the interference of CMM with their daily functioning from 40 to 100% in the VAS-Function scale.

Gabapentin has been shown to have central sites of pharmacological action, including calcium channels and possibly NMDA receptors [42-46] These pharmacological targets seem to be also involved in the pathophysiology of CMM [3 4 47]. The results of this study leave room to think that gabapentin may provide its analgesic effect in CMM by acting on such targets. However, further extensive research is required in both of these areas (the pathophysiology of CMM and gabapentin's analgesic mechanism of action), since none of these two processes are completely understood to date. The results of this clinical trial support the hypothesis that CMM may have important CNS effects[47] as one of the mechanisms that influence this condition. It is known that gabapentin has important central sites of action [48-50] and this may be significantly related to its effect. However, there are also few recent reports suggesting the analgesic action of gabapentin in peripheral sites [51 52] and in postoperative pain [53]. Therefore more research on the peripheral action of this drug is required before making definitive conclusions on this statement.

There are no previously published studies in the literature evaluating the analgesic effect of gabapentin on any type of chronic TMD. Central-acting pharmacological agents most commonly

utilized for managing chronic masticatory muscle pain are TCAs. Like TCAs, gabapentin also acts centrally, although through different mechanisms of action.

Pain reduction with gabapentin in subjects suffering from CMM identified in the present study is similar to reported pain reduction with the use TCAs. A recent RCT conducted by Rizzatti-Barbosa et al in 2003 [54] demonstrated that amitriptyline at 25mg/day is an effective management option for treating chronic TMD pain. Amitriptyline produced a statistically significant pain reduction on the VAS of 75% in the treated group in comparison to 28% in the control group. Unfortunately, this study did not differentiate if the chronic pain was of muscular or articular origin a combination of both entities. Plesh et al [55] compared the effect of a 6 week trial of amitriptyline 30mg/day between a group of subjects with chronic TMD myofascial pain and a group presenting a combination of chronic myofascial and articular (TMJ) pain. They reported a VAS pain reduction from 6.2 to 3.1 (50%) in the myofascial group and 5.6 to 2.9 (48.21%) in the combined group. However, this trial did not have a control group and careful interpretation of these results is recommended. Sharav et al [56] conducted a 4-week randomized controlled clinical trial, in which amitriptyline was reported effective to manage chronic facial pain with doses ranging from 50 to 150mg per day. The pain score difference from baseline on the 10cm VAS was measured to be 27.8mm in the amitriptyline group and 2.3mm in the placebo group. Lower doses of amitriptyline did not show a statistically significant difference in comparison to placebo when evaluating pain reduction on the VAS. There was however, statistically significant pain reduction based on the McGill Pain Questionnaire. Unfortunately, this study failed to differentiate if the pain was myogenous, articular or combined myogenous and articular in origin.

When choosing pharmacotherapy, the side effect profile and interaction of the treatment medication with other medications should be considered. Unfortunately, previously published studies regarding TCA treatment in TMD did not provide statements regarding the frequency of side effects and associated withdrawals. However, it is known that the dose of TCA is usually limited by anticholinergic side effects, such as dry mouth, constipation, blurred vision and urinary retention [57] [58]. Cardiovascular side effects such as postural hypotension or serious ventricular arrhythmias can also occur, especially in those subjects with pre-existing heart disease [57] [58]. One RCT performed by Heymann et al [59] comparing the analgesic effect of amitriptyline and nortriptyline in subjects with fibromyalgia reported the incidence of side effects for both medications. The incidence of side effects reported with amitriptyline 25mg was dry mouth (10%), abdominal pain (10%), changes in taste (5%), drowsiness (2.5%), dizziness (2.5%), nausea (2.5%), weight gain (2.5%), and apathy (2.5%). The incidence of side effects of nortriptyline 25mg were dry mouth (15.8%), abdominal pain (18.4%), changes in taste (5.3%), drowsiness (2.6%), dizziness (10.5%), nausea (2.6%), apathy (5.3%), palpitation (7.9%), sweating (2.6%), migraine (5.3%), memory deficit (2.6%)and diffuse pain (2.6%). The number of side effects of gabapentin reported in our trial was slightly lower than the reported by Heymman et al for TCA. In Heyman's study, the drop out rate due to side effects was 5.1% of subjects in the nortriptyline group. Drop outs were not observed in the amitriptyline and placebo groups. In our clinical trial, the withdraw rate due to side effects was 4% for the gabapentin as well as for the placebo group.

A major advantage of gabapentin over TCA is its lack of major interactions with other drugs [36] [60] [61]. In contrast it is well known that TCA are involved in several clinically important drug interactions. They can cause severe CNS toxicity if administered along with monoamine oxidase inhibitors

(MAOI) [62]. TCA drugs are also known for potentiating the effect of alcohol and probably of other sedatives [62]. TCAs inhibit the uptake of epinephrine by sympathetic nerve endings and can potentiate the cardiovascular effects of epinephrine. Therefore, from a dental practice perspective, caution should be taken with patients taking TCA when using epinephrine contained in local anesthetics and gingival retracting cords [62 63]. Gabapentin is not metabolized and therefore there is no risk of hepatic or renal damage.

In addition, it is not uncommon to see in clinical practice that some patients are reluctant to take TCAs. Although prescribed for chronic pain in clinical practice, patients can resist taking "antidepressant medications" because of social stigma. Many patients taking TCA report excessive drowsiness during the first hours of the morning and they often discontinue the treatment. In this trial the drowsiness detected in gabapentin patients was not significantly different than in the placebo group and social stigma due to "antidepressant therapy" is not a concern with gabapentin when recommending its use in clinical practice.

In this study, gabapentin has been proven effective to treat CMM. It should be considered as another treatment option for this condition with a cleaner drug interaction profile and less number of side effects than TCA agents.

NSAIDs and muscle relaxants are often palliative in the treatment of chronic musculoskeletal conditions. However, the long-term use of NSAIDs in the treatment of CMM is limited by two reasons. Firstly, the use of NSAID drugs long term is not supported in the literature [64] and are best used short term due to their side effect profile. The gastrointestinal side effects of these agents are

well known and it is reported that over 2% of patients that take NSAIDs followed over five years are at risk of developing peptic ulceration [65]. However, it is important not to forget that the anti-inflammatory effect is not the only mechanism through which NSAIDs provide analgesia, and they can often be quite helpful as palliative agents when used intermittently as adjuvant agents in combination with central-acting medications [66]. Secondly, the presence of inflammation in chronic muscle pain is controversial. Studies have shown that inflammation is not present in muscle tissue with chronic pain [67 68]; therefore it is thought that inflammation may not the main problem that causes pain symptoms in chronic orofacial muscle disorders. In addition, central-acting medications have been proved superior to NSAIDs in the treatment of chronic orofacial pain [69] and there is reported evidence of no efficacy of NSAIDs in other chronic musculoskeletal conditions, such as fibromyalgia [70]. However, other studies report the presence of local inflammatory substances in the masticatory muscles of patients with CMM [13 71].

Muscle relaxants are also often used as palliative agents in the treatment of chronic musculoskeletal pain. The use of some of these agents, such as cyclobenzaprine is best used in short-term therapies but may be used intermittently for chronic conditions [65]. In addition, the analgesic efficacy of these medications seems to be limited when used long term. Muscle relaxants have showed limited effectiveness for chronic neck pain and for chronic low back pain when used for up to 4 weeks [70]. Most muscle relaxants have a central effect that sedates patients, rather than acting directly on the muscle tissue, which may explain positive response of some patients [72]. These medications should be use only for palliative and intermittent use. The sedative side effects of muscle relaxants causes drowsiness in 29% to 39% of patients, which limit their use long term, as it may interfere with daily activities.

From a dental practice perspective, the general dentist and orofacial pain specialist should be aware of the multifactorial nature of chronic pain in the masticatory muscles [5 1 2 9] and direct treatment accordingly. These clinicians should have a working knowledge of a number of different classes of drugs, such as gabapentin and TCAs. Because CMM does not appear to have an occlusal etiology or pathophysiology [1 2 5], peripheral treatments, such as irreversible occlusal therapies are not appropriate. This is supported using evidence based medicine. Systematic literature reviews did not identify sufficient evidence to support occlusal therapy (such as prosthodontics, orthodontics or occlusal adjustments) as a general method for treating non-acute TMD [73]. In addition, there is weak evidence to suggest that occlusal conditions are related to TMD [74]. The least invasive and least expensive treatment approaches available should be undertaken. Splint therapy has been proved to be effective in treating masticatory muscle pain [75-77], however when the pain becomes chronic, splint appliances become part of a multidisciplinary treatment approach, rather than a unique and general management option. [1]

The results of this clinical trial suggest that gabapentin may be effective in the treatment of other chronic musculoskeletal problems. Fibromyalgia represents a chronic muscular problem that has CNS and peripheral influences, psychological implications and sleep disturbances [78] which like CMM, may respond to gabapentin therapy. This treatment approach is supported by one study which reported that gabapentin was effective in 35% of subjects with intractable chronic musculoskeletal pain [79]. In addition, an open-label pilot study showed that gabapentin in combination with a topical lidocaine patch 5% was effective in decreasing chronic low-back pain levels [80]. However, to date, there are no clinical trials evaluating the analgesic efficacy that

gabapentin may have on specific chronic musculoskeletal disorders. Further clinical trials performed in a well-controlled fashion are required to begin exploring the analgesic action of gabapentin in chronic musculoskeletal disorders.

2.5 CONCLUSIONS

The following conclusions are based on the results of this RCT:

- Gabapentin is an effective pharmacological therapy for reducing pain reported by subjects experiencing CMM. The analgesic effect of gabapentin was significantly superior to placebo.
- Gabapentin is superior to placebo for reducing hyperalgesia in the masticatory muscles in subjects with CMM.
- Daily functioning improves with gabapentin therapy in subjects with CMM.
- In addition, we have also demonstrated that pain reduction reported with gabapentin therapy in CMM subjects has a positive linear relationship with a decrease of clinical hyperalgesia.

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chapter 3: GENERAL DISCUSSION AND RECOMMENDATIONS

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3.1 GENERAL OVERVIEW OF THE STUDY AND CLINICAL IMPLICATIONS

Chronic pain has a significant prevalence in the general population [1], reflecting a socioeconomic problem for patients and the health care system [2 3]. Forty percent of cases seen in chronic pain clinics suffer pain in the head and neck regions [4], indicating that orofacial pain is a significant problem in this subject population. Orofacial pain includes a number of conditions, including TMD. At the same time TMD implies different categories with sub-diagnosis, including CMM [5 6].

CMM is known as constant pain in the masticatory muscles for more than six months. It may originate from untreated inflammatory or acute conditions [6] or it may have no obvious initial cause. Like other chronic pain conditions, CMM can affect quality of life of patients. When pain becomes chronic, its treatment also becomes more complicated. Multidisciplinary treatment is required to approach the problem from different perspectives at the same time. Pharmacological treatment is an important key tool for treating chronic pain. In the field of orofacial pain, there is a need of more research evaluating the effectiveness of new pharmacological options. Most of the clinical pharmacological treatment of chronic TMD problems is based on clinical experience and literature reports with low levels of evidence [7].

It is thought that CMM receives CNS inputs, as one of the elements that may maintain the pain [6] in this condition[8 9], therefore central acting drugs like TCAs have been used in clinical practice for its management. The second-generation antiepileptic agent, gabapentin, has been used in the management of different types of chronic pain conditions and seizure disorders. However, there were no previous RCT providing high levels of scientific support to the treatment of CMM with gabapentin. Although previous research does provide evidence for use of TCAs[10] in chronic muscle pain conditions, gabapentin appears to be also effective in this condition with a milder side effects and drug interaction profile.

In this randomized controlled study, the efficacy of gabapentin was evaluated on female subjects with CMM. Three main outcome measures were assessed: CMM pain intensity reported on a VAS, number of tender palpation sites in the masticatory muscles based on the PI, and the VAS report of how CMM affected the daily functioning of these subjects. This study ran for 12 weeks utilizing doses ranging from 300mg to 4200mg per day. At the end of the study, subject treated with gabapentin reported a significant CMM pain reduction on the VAS. They also demonstrated less tender sites in the masticatory muscles when they were palpated with an algometer. Finally, they also reported that since the pain levels diminished, its interference with their daily routine decreased significantly as well.

These results have strong clinical implications for the fields of medicine and dentistry. From a medical perspective, gabapentin may represent a promising treatment option to manage other chronic musculoskeletal problems with similar pathophysiology of CMM. For example, it may represent a treatment option in those cases in which an overlap of CMM and fibromyalgia is

present [11] [12]. Gabapentin has been used successfully for the treatment of chronic neuropathic pain problems such as post-herpetic neuralgia, painful diabetic neuropathy, reflex sympathetic dystrophy, painful HIV-related peripheral neuropathy and neuropathic cancer pain [13]. Based on the results of the present study it would be appropriate to assess the analgesic action of gabapentin in other chronic musculoskeletal conditions such as low-back pain and fibromyalgia.

The drug pregabalin is an analog of GABA, which has been developed as a follow-up compound to gabapentin. It acts in a similar way blocking calcium channels and increasing GABA in the brain. It has already been tested for different neuropathic pain conditions [14]. Due to similar mechanisms of action to gabapentin, pregabalin may be a useful agent to evaluate in RCT for centrally mediated muscle pain problems like fibromyalgia and CMM. Furthermore, it will be very valuable to conduct RCTs comparing the analgesic effect and side effect profile of gabapentin and pregabalin to determine possible therapeutic advantages and disadvantages between both drugs.

From a dental perspective, the present study provides support to confirm that the pathophysiology of CMM is unrelated to occlusal factors, and should further discourage expensive irreversible occlusal treatment approaches that aim to address unrelated etiologies to this condition.

This study has not evaluated other treatment options which may have potential benefit in CMM. Psychologic intervention, management of sleep quality, and acupuncture may serve as non invasive treatment options. Multidisciplinary treatment may ultimately provide the best treatment outcome.

3.2 LIMITATIONS

The main limitation of this study is related to the measuring method for pain interference with daily functioning and quality of life. Although it was not the primary interest of investigation in this study, an attempt was made to obtain a general idea on how CMM was interfering with the subject' daily functioning. For this purpose a 10cm VAS was utilized asking the subject to indicate how the pain was interfering with their daily functioning and performance of day-to-day activities.

It could be argued that more valid and reliable research tools are available to measure how pain affects quality of life and daily functioning. Methods like the McGill Pain Questionnaire, The Medical Outcomes Survey-Pain Index and methods for grading chronic pain severity developed by Von Korff et al. are recommended as a first line research tools to evaluate psychological implications associated to dysfunctional pain [15] [16-18]. These methods are mainly used to assess chronic pain syndromes. Chronic pain syndrome implies psychological implications that are related to the chronic pain symptoms [5] [16]. However, this study was mainly focused on the analgesic effect of gabapentin on chronic pain itself in general, and disability associated with chronic pain is not necessarily always related to psychological impairment [5]. The diagnostic criteria utilized in this study did not screen for depression, anxiety or disability often associated with chronic pain. Although the VAS-functional outcome measure used in this study did demonstrate statistically significant difference between the placebo and gabapentin groups, the impact on daily functioning should be interpreted with caution. However, it is important to mention that no functional index has been developed specifically for orofacial pain patients or chronic TMD problems. Therefore, many elements of the pre-existing questionnaires and tools to assess daily function and chronic pain

impact on quality of life are designed for chronic pain in general and may not necessarily apply to orofacial pain patients.

In this clinical trial, subjects were provided with a 30-day diary every follow-up visit in order to record the amount of acetaminophen taken for break through pain. However, 20 (55.55%) subjects were not compliant at returning the record dairy for each visit. For this reason, the data derived from these diaries was not considered reliable enough to use as an indirect tool to measure the analgesic efficacy of the gabapentin in comparison to placebo, based on the amount of acetaminophen taken for break-through pain.

Based on this experience we recommend further clinical trials in which subjects are better educated in terms of the importance of counting the amount of rescue drug utilized during the study. They should understand that this drug, more than being just a palliative pain medication for the trial, is also an important tool to assess indirectly how the study medication is acting on their symptoms. For future clinical trials rescue medication should be dispensed to subjects in blister-packs, from which they could take the medication when required. This may be a more practical tool than medication diaries, which subjects may forget to fill out every time there is a need to take rescue medication. Returning blister-packs at each follow-up visit may help the investigator to count the medication left since dispensed at the initial visit. This is an easier way for the investigator and for the subject to have better control over the rescue medication, rather than just having in it bottles where is usually more difficult to count the amount of tablets that are not consumed.

3.3 RECOMMENDATIONS FOR FUTURE RESEARCH

The pathophysiology of chronic muscle pain is very complex and is not yet fully elucidated. This, without doubt, is reflected in the clinical practice of chronic pain management strategies. Further research at a basic science level is required in order to enrich our current and limited understanding of the pathophysiology of CMM. This would eventually provide the clinical pharmacology field with new possible targets for chronic muscle pain management, as well as with a better understanding of the function of those we already know. Most of the basic science experiments studying the pathophysiology of central pain are focused on neuropathic pain. More studies of this type are recommended specifically evaluating chronic musculoskeletal pain in order to determine the main difference between chronic neuropathic and muscle pain in their mechanisms of action.

The author of this thesis also recommends and encourages conducting more research regarding chronic interventional strategies for chronic orofacial pain. Orofacial pain is a very broad and complex term that involves TMD, headaches and neuropathic facial pain. A big part of pharmacological management is a result of clinical experience, case reports and open-label studies. RCTs provide the highest level of evidence for determining the efficacy of an interventional therapy [19]. The field of orofacial pain is in need of well-controlled clinical trials to provide solid scientific support for clinical practices that have been utilized up to date. The TMD area in particular, needs to be further explored in terms of pharmacological management in order to determine which available options work more efficiently with minimal negative effects.

Another important recommendation is that future studies should define the type of pain that is evaluated. Most of the studies, whether they are epidemiological or clinical trials assessing therapies, indicate TMD pain as the problem being evaluated. It is important to remember that the term TMD itself is not a specific diagnosis since it can involve pure myogenous pain, articular (TMJ) pain and a combination of both. For instance, pain in the TMJs derived from degenerative joint disease or from mechanical problems has a very different pathophysiology than CMM or myofascial pain; therefore they are completely different entities [6]. For this reason, each sub-diagnosis under TMD can be very different from each other in terms of pathophysiology and also prevalence in the general population. In addition, TMD problems can also be acute, chronic, inflammatory or centrally mediated. This adds another need for differentiation when conducting a study, since they all have different biological mechanisms that would respond differently to a variety of available drugs. These diagnostic specifications would allow us to determine the best therapies for each type of TMD and orofacial pain condition.

Finally, in terms of gabapentin therapy, further studies evaluating the role of gabapentin on sleep quality will be helpful in the management of chronic pain, which is often associated with poor quality of sleep. In particular from an orofacial pain perspective, the evaluation of the effect of gabapentin on sleep bruxism will be of great value. There are literature reports suggesting a suppressive action of gabapentin on sleep bruxism [20]. This may be the "tip of the iceberg" for future research approaches evaluating to what degree gabapentin may help suppressing sleep bruxism, as a centrally originated parasomnia that is significantly involved in orofacial pain problems.

Long term studies with gabapentin are required to determine if pain reduction will continue to decrease over time with sustained dosage. It also remains unknown if gabapentin will restore normal central nervous system pain modulation. Long term studies evaluating pain levels in subject when gabapentin is withdrawn are required.

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appendices

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APPENDIX 5

"Analgesic action of gabapentin on chronic pain in the masticatory muscles"
TMD/Orofacial Pain Clinic – University of Alberta

Initial Evaluation.

Visit num. _____ Date_____
Patient Name: _____
Date of Birth: ___ /___ / ___ Gender: ___M / ___F
Physician's name: _____
Chief Complaint: _____
Onset: _____
Reported masticatory muscle pain: VAS_____

Medical Antecedents

_____
_____
_____
_____

Current Medications

_____
_____
_____
_____

Screening Intraoral Exam

Soft Tissues

___salivary glands ___tongue ___Floor of mouth
___palate ___buccal mucosa ___gingiva
___periodontal disease

Dentition

___percussion sensitive ___dental infection ___tooth decay

TMJ

Right: sounds: _____ / Pain: ___ Left: sounds: _____ / Pain: ___

Range of Motion

Voluntary Opening: ___mm / Lateral Excursions R___mm – L___mm / Protrusive: ___

Self report for pain intensity (1 week average): VAS_____

Self report of pain impact on quality of life and normal activities: VAS_____

Masticatory Muscles Palpation

Palpation

0 = none. 1 = mild. 2 = moderate. 3 = severe

Extraoral

( )R L( ) Ant. Temporalis
( )R L( ) Mid. Temporalis
( )R L( ) Post. Temporalis
( )R L( ) Masseter (deep belly)
( )R L( ) Masseter (superficial belly)
( )R L( ) Masseter (superficial inf. belly)
( )R L( ) Med. Pterygoid
( )R L( ) Post. Digastric
( )R L( ) Lat Pterygoid (protrusive resistance)
( )R L( ) Vertex – Reference

Intraoral

( )R L( ) Temporalis Insertion

Neck

( )R L( ) Sup. SCM
( )R L( ) Mid. SCM
( )R L( ) Inf. SCM
( )R L( ) Trapezius Occipital
( )R L( ) Upper Trapezius
( )R L( ) Posterior Cervical

Joint Capsule

( )R L( ) Lateral
( )R L( ) Posterior

Comments:

Next Visit

In order to establish the best medication to treat patients suffering chronic jaw muscle pain carefully designed scientific studies are required. To be valid, the study must randomly assign patients into groups (like the flip of a coin). Each group is provided with a specific medication to take for the duration of the study. To prevent bias the investigator and patient will not know what medication they are given until the end of the study.

The purpose of this study is to evaluate the effectiveness of gabapentin in treatment of chronic jaw muscle pain. We plan to evaluate if this medication will reduce your pain.

Procedure:

Your participation in this study will involve the following steps:

1. You will be contacted by telephone to explain the project to you and to see if you are eligible to participate. If you agree to participate an examination appointment will be set up. You will be provided with parking coupons to cover the cost of parking at the University.
2. The first appointment will involve reviewing the study information form. If you would like to participate you will be asked to sign a consent form. You will also be asked to provide permission for us to contact your physician to ensure your health is stable and that there is no medical contraindication for you to participate in this study. You will be asked to report your average pain intensity for the last week in a 1-10 scale. You will be also asked to report how this pain has affected your daily activities in a 0-10 scale.
   A 10 - 15 minute examination will be completed. This examination will involve checking your jaw muscles, measuring your range of jaw opening and checking the inside of your mouth.
   If you are eligible to participate in this study a second appointment will be scheduled. You will be asked to discontinue all pain medications for approximately 2 weeks prior the second appointment. It is very important to be off other pain medications prior to starting this study. Medications such as certain antidepressants or benzodiazepines will be allowed as long as these medications have been taken on regular basis. No changes in the dosage of these medications will be allowed during the course of the study.
3. At the second appointment, lasting approximately 15 minutes, you will be asked to report the intensity of your pain and its impact on your normal activities. A clinical examination will be performed. In this examination the investigator will check your jaw muscles with a special device called a

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APPENDIX 7

CONSENT FORM

Title of Project: **Analgesic action of gabapentin and placebo effect on chronic pain in the masticatory muscles: a randomized controlled clinical trial**

TMD/Orofacial Pain Clinic – University of Alberta
Investigator: Dr. Pablo M. Kimos
Supervisor: Dr. Paul Major

Please circle the answer:

Do you understand that you have been asked to be in a research study?

Yes No

Have you read and received a copy of the attached information sheet?

Yes No

Do you understand the benefits and risks involved in taking part in this research study?

Yes No

Have you had an opportunity to ask questions and discuss this study?

Yes No

Do you understand that you are free to refuse to participate or withdraw from the study at any time? This will not affect your care.

Yes No

Has the issue of confidentiality been explained to you? Do you understand who will have access to your records?

Yes No

Do you understand that your physician would be contacted in order to determine if your are able to take the medications used in this study?

Yes No

This study was explained to me by: _____

I agree to take part of this study.

_____ _____ _____
Patient's signature Date Witness

_____ _____
Printed name Printed name

I believe that the person signing this form understands what is involved in the study and voluntary agrees to participate

_____ _____
Investigator's signature or Designee Date

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PATIENT

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APPENDIX 8

FAMILY PHYSICIAN CONSENT FORM

Analgesic action of gabapentin and placebo effect on chronic pain in the masticatory muscles: a randomized controlled clinical trial

Investigator: Dr. Pablo M. Kimos
Supervisor: Dr. Paul Major.

We acknowledge that _____ qualifies for participate on this study. We acknowledge that we know the patient's clinical status and that there are no medical contraindications or exclusion criteria to prohibit enrolling the patient.

_____ _____
Name of physician Signature

_____ _____
Name of physician Signature

Date: _____

Please inform our clinic if there is any change in this patient's medical conditions or prescribed medication

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APPENDIX 9

"Analgesic action of gabapentin on chronic pain in the masticatory muscles"
TMD/Orofacial Pain Clinic – University of Alberta

Patient Data Collection Sheet

Visit num. _____ Date_____
Patient Name:_____
Date of Birth: ___ /___ /___ Gender: ___M / ___F
Physician's name: _____
Chief Complaint:_____
Onset:_____

Self report for pain intensity (1 week average): VAS_____

Self report of pain impact on quality of life and normal activities: VAS_____

Masticatory Muscles Palpation

Temporalis	Masseter
1) Anterior (nv= 1.84 kg/cm²)	4) Superficial anterior (nv= 1.51 kg/cm²)
Right PPT_____ 1 / 0	Right PPT_____ 1 / 0
Left PPT_____ 1 / 0	Left PPT_____ 1 / 0
2) Medial (nv= 2.17 kg/cm²)	5) Superficial inferior (nv= 1.40 kg/cm²)
Right PPT_____ 1 / 0	Right PPT_____ 1 / 0
Left PPT_____ 1 / 0	Left PPT_____ 1 / 0
3) Posterior (nv= 2.26 kg/cm²)	6) Deep (nv= 1.54 kg/cm²)
Right PPT_____ 1 / 0	Right PPT_____ 1 / 0
Left PPT_____ 1 / 0	Left PPT_____ 1 / 0

Positive responses: _____/12 = _____ (final palpation index score)

Reported Side effects

___Drowsiness	___Dizziness	___Fatigue
___Dry Mouth	___Cardiac changes	Other_____
___Weight gain	___Blurred vision	_____
___Appetite changes	___Urinary retention	_____
___Constipation	___Memory & cognitive dysfunction	_____

Comments_____
_____
_____

Tylenol left since last visit: _____

Next Visit:_____
_____
_____

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APPENDIX 10

"Analgesic action of gabapentin and placebo affect on chronic pain in the masticatory muscles: a randomized controlled clinical trial"

TMD/Orofacial Pain Clinic - University of Alberta

No serious side effects have been reported with the use of gabapentin. However, it is very important for us to monitor your health status in regard to the use of this medication, during your participation in this clinical trial. Therefore you are asked to report in this record sheet any possible side effects that you could experience, during the 30 days period before your next visit to our clinic.

You have been provided with enough Tylenol tablets (500mg) for 30 days. You are allowed to take this medication in case of any residual pain. If this is the case, Tylenol must be taken as needed, with a maximum of 8 tablets per day.

INSTRUCTIONS

- Please report, on the reverse, if you experience any side effect during the 30 days period before your next visit to our clinic.
- If you need to take Tylenol during this period, please report on the reverse, the day and the number of tablets taken.

Day 01 side effects: # Tylenol ___	**Day 02** side effects: # Tylenol ___	**Day 03** side effects: # Tylenol ___	**Day 04** side effects: # Tylenol ___	**Day 05** side effects: # Tylenol ___
Day 06 side effects: # Tylenol ___	**Day 07** side effects: # Tylenol ___	**Day 08** side effects: # Tylenol ___	**Day 09** side effects: # Tylenol ___	**Day 10** side effects: # Tylenol ___
Day 11 side effects: # Tylenol ___	**Day 12** side effects: # Tylenol ___	**Day 13** side effects: # Tylenol ___	**Day 14** side effects: # Tylenol ___	**Day 15** side effects: # Tylenol ___
Day 16 side effects: # Tylenol ___	**Day 17** side effects: # Tylenol ___	**Day 18** side effects: # Tylenol ___	**Day 19** side effects: # Tylenol ___	**Day 20** side effects: # Tylenol ___
Day 21 side effects: # Tylenol ___	**Day 22** side effects: # Tylenol ___	**Day 23** side effects: # Tylenol ___	**Day 24** side effects: # Tylenol ___	**Day 25** side effects: # Tylenol ___
Day 26 side effects: # Tylenol ___	**Day 27** side effects: # Tylenol ___	**Day 28** side effects: # Tylenol ___	**Day 29** side effects: # Tylenol ___	**Day 30** side effects: # Tylenol ___

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APPENDIX 11

"Analgesic action of gabapentin on chronic pain in the masticatory muscles"
TMD/Orofacial Pain Clinic – University of Alberta

Telephone follow-up record sheet

Date:_____ (week num:_____) ——— Next visit: _____

CURRENT DOSE:_____per day

Side Effects reported by the patient (please record onset date and behavior)

_____
_____
_____
_____
_____
_____
_____
_____
_____

In case of needed Tylenol:
Each time you need to take Tylenol, please report when you took it and how many tablets

_____
_____
_____
_____
_____
_____

DOSE INCREMENT:_____ per day NEW DOSE (total):_____ per day
Comments -

_____
_____
_____